Journal of Pediatric Surgery 59 (2024) 1886–1891

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.sciencedirect.com/journal/journal-of-pediatric-surgery

Patterns and Outcomes in Pediatric Abdominal Tuberculosis: A Single Centre Cohort Study

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A R T I C L E I N F O

Article history:
Received 3 January 2024
Received in revised form
15 March 2024
Accepted 14 April 2024

Keywords:
Abdominal tuberculosis
Pediatric
Surgery
Outcomes

A B S T R A C T

Introduction: Abdominal tuberculosis presents in a variety of ways. Different testing modalities must be applied in addition to having a high clinical suspicion to diagnose and initiate therapy. Medications have a good response; however, morbidity has been seen following surgical management of complicated presentations like intestinal obstruction and perforation. There is a paucity of studies in the pediatric age group which evaluate response to the different treatment regimen and identify factors associated with poorer outcomes in children with abdominal tuberculosis.
Methods: Patient records of 75 children with abdominal tuberculosis at a single center were evaluated using a questionnaire, covering a 14-year period from 2007 to 2021. Demographic features, presenting signs and symptoms, investigations and treatment details were studied. In- person or telephonic follow-up was conducted to identify treatment outcomes.
Results: Incidence of abdominal TB was 7%, of all TB children with a mean age of 10.1 years. Mesenteric lymph nodes were involved in 67% and small intestine in 33% cases. Surgery was required in 22 children. 85% children completed treatment. Small intestine involvement had higher probability of undergoing surgery. Of the 70 children with complete follow up, 64 were well and 6 children succumbed to the disease. Older age, small intestine involvement and surgery were independently associated with higher mortality.
Conclusion: Intestinal involvement is associated with greater need for surgical intervention and greater mortality. Adolescents have poorer outcomes. Further studies are required focusing on these individual subgroups to understand the patterns of presentation, causes for mortality and prevention.
Level of Evidence: Level 5.

1. Introduction

Children represent one-tenth of the global annual incidence of 10 million cases of Tuberculosis (TB), with an additional 0.7 million cases seen among adolescents per year.

In children below the age of 15, TB continues to be among the 10 leading causes of death with 2,50,000 children dying of tuberculosis worldwide every year [1].

Globally, 80% of the children dying of tuberculosis are below the age of five years, while more than half (55%) of the total estimated cases are not even reported [2,3].

Abdominal TB may be defined as TB infection of the gastrointestinal tract, peritoneum, abdominal lymph nodes or the solid viscera [4]. Abdominal TB has been long causing many dilemmas to clinicians, due to its insidious presentation.

While surgery is not the preferred option for surgeons, in many cases there is no option and high morbidity and/or mortality has been reported following emergent surgery. Prolonged and difficult treatment in children with TB who have peritonitis or obstructive symptoms is an additional challenge [5,6].

Abbreviations: TB, Tuberculosis; ATT, Anti Tubercular Treatment; RNTCP, Revised National Tuberculosis Control Program; WHO, World Health Organization; PCR, Polymerase Chain Reaction; CB-NAAT, Cartridge based Nucleic Acid Amplification Test; DOTS, Directly Observed Anti Tubercular therapy.

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https://doi.org/10.1016/j.jpedsurg.2024.04.006
0022-3468/

Medical management of TB is quite effective and consists essentially of Anti Tubercular Treatment (ATT). In India this is given according to the Revised National Tuberculosis Control Program (RNTCP) in accordance with the World Health Organization (WHO) guidelines [7].

2. Need for the study

Abdominal tuberculosis in children has been studied less than in adults. Evaluation of factors associated with poorer outcomes and the role of surgical interventions is poorly documented in children. We need more studies focusing on children and the surgical aspects in order to identify these factors and work towards improving outcomes.

Through this observational study we aimed to contribute to the knowledge of the pattern of presentation of the pediatric patients with abdominal TB in our tertiary care center in north-western India as well as to report survival outcomes.

3. Methodology

Pediatric patients up to the age of 18 years, diagnosed with abdominal TB in the 14-year study period (2007–2021) in our institution were included in this observational cohort study.

Institutional ethics approval (IECCMCL/01–0162020) was obtained.

The study is being reported according to STROBE guidelines.

Data related to demography, clinical signs and symptoms, investigations, treatment and outcomes were recorded as per a pre-approved protocol from patient and medical records.

Outcome data were collected from medical records, direct interviews at follow-up visits or telephonic interviews. During to the Covid-19 pandemic at the time of the study, a majority of our patients were unable to come for in-person follow-up visits, so their data were collected over telephonic follow-up using a standard and pre-decided questionnaire in the local language and a verbal consent. The minimum follow up period was 2 years since diagnosis.

A diagnosis of abdominal TB was reached on the basis of strong and consistent clinical suspicion, laboratory and histopathological findings or radiological evidence consistent with abdominal TB. In some cases, a diagnosis was made based on operative findings. Children who were empirically started on ATT but later found to have an alternate diagnosis were excluded from the study.

Laboratory microbiological investigations included a Mantoux test (which measures the degree of delayed cellular hypersensitivity to tuberculin), body fluid or tissue mycobacterial cultures and TB DNA PCR (Polymerase Chain Reaction) using the Cartridge based Nucleic Acid Amplification test (CB-NAAT) also called Gene Xpert® MTB/RIF which is an automated cartridge based molecular technique useful in detecting tuberculosis at an early stage as well as for indicating drug resistance which was done in 30 patients [8].

4. Statistical analysis

Statistical analysis of study data was conducted under the guidance of the Surgical Statistics Hub (Johannesburg, South Africa), under the auspices of the NIHR Global Health Research Unit on Global Surgery.

The full study dataset was entered into a MS Excel spreadsheet and imported into STATA Version 16.0 suite of analytics software. The Shapiro–Wilk W test was performed to determine the normality of data distribution. Descriptive statistics were performed for all study participants and reported as means and standard deviations (SD) or median values with interquartile ranges (IQRs), depending on the distribution of the continuous data, or as frequencies and percentages for categorical data. The grouping of patients for the outcome variables of mortality (dead vs alive), surgical intervention, parental literacy and household income were assessed using the non-parametric Mann–Whitney U tests and the Pearson's Chi-squared with Fishers' exact test, as appropriate. A 5% level of significance was considered statistically significant.

All children in the study had a minimum of 2 year follow up. Children with incomplete follow up were not included in the follow up data analysis.

5. Results

During the study period 1067 pediatric patients were diagnosed with TB in our hospital out of which 75 children with a mean age (±SD) of 10.1 (4.9) years had abdominal TB. There was a slight preponderance in the second decade of life and a male preponderance**.** Large families (at least five members) constituted more than half of our cohort (56%) and less than half of the families had fixed incomes. Most of our patients came from literate families (80%), with literacy being defined as a person aged seven years and above who can both read and write with understanding in any language (Table 1). Twenty-six (34%) patients had a history of prior TB contact and most patients in our group (95%) had received a BCG vaccination.

The children in this cohort had a combination of signs and symptoms with a median (IQR) duration of symptoms of 30 (7–90) days (Table 2).

Thirty-four (45.3%) children reported low grade fever as the commonest symptom with a median (IQR) duration of 15 (7–60) days, followed by signs of obstruction (constipation and/or vomiting) in 15 (20%) of patients at and weight loss in 9 (12%) patients. Abdominal tenderness (n = 27; 36%) at presentation was the most common sign. There were no significant differences in the clinical presentation across the age groups.

The Mantoux test was positive in 56.4% of 39 patients. Nine (30%) patients had a positive TB DNA PCR. A culture positive for

Table 1
Demographic and socioeconomic characteristics.

Parameter	n (%)
Age, years	
Mean (±SD), 10.8 (4.9)	
Categories:	
1–5 years	18 (24.0%)
6–10 years	18 (24.0%)
11–15 years	26 (34.7%)
16–18 years	13 (17.3%)
Gender	
Male	39 (52%)
Female	36 (48%)
Family size	
≥5 members	42 (56%)
>3 members	24 (32%)
≤3 members	9 (12%)
Income	
Fixed	35 (46.7%)
Non-Fixed	40 (53.3%)
Literacy status of parents	
Both Literate	53 (70.7%)
One Literate	7 (9.3%)
Both Illiterate	15 (20%)

Table 2
Presenting signs and symptoms.

Parameter	n (%)	Median Duration Of Symptoms (IQR) in Days
Anorexia	5 (6.7%)	30 (30–90)
Constipation	7 (9.3%)	10 (5–90)
Vomitting	8 (10.7)	3 (2–30)
Cough	3 (4%)	120 (60–497)
Diarrhoea	4 (5.3%)	75 (30–135)
Fever	34 (45.3%)	15 (7–60)
Malaise	5 (6.7%)	30 (10–30)
Weight loss	9 (12%)	125 (90–180)
Symptoms		
Abdominal Distention	10 (13.3)	
Abdominal Mass	1 (1.3)	
Abdominal Tenderness	27 (36)	

Mycobacterium TB was seen in only one child out of the 16 who had a culture done.

Fifty-six of 58 children showed evidence of enlarged lymph nodes, ascites, hepatosplenomegaly and/or intestinal obstruction on ultrasound. CT abdomen was done for 13 patients and all showed various findings suggestive of abdominal TB including abdominal mass, bowel wall thickening, omental thickening intestinal obstruction, ascites and hepatosplenomegaly. In twenty-three patients a histopathological diagnosis of abdominal TB was made.

Mesenteric lymph nodes (n = 47; 63%) were the most common site of involvement in the abdomen, while the small intestine (n = 25; 33.3%) especially the distal ileum (n = 19) was the most common hollow viscus involved. The median duration of symptoms in children with small bowel disease did not differ to those with other abdominal sites (p = 0.40).

The mean (±SD) age of children having involvement of the small intestine was 11.0 (5.0) years, slightly higher than the mean age (9.5 ± 4.5 years) of those having lymph node involvement, though not a statistically significant difference.

Surgical intervention was needed in twenty-two children (29.3%). Procedures included diagnostic operations, diversion stomas, perforation closure and bowel resection anastomoses (Table 3). Children with small bowel involvement had a significantly a higher chance of having an operation (72%) than being managed conservatively when compared to those children without small bowel involvement at 8% (p = 0.001).

Five children had postoperative complications after the primary procedure which included enterocutaneous fistulas (n = 4) or anastomotic leak with three children needing operative management of the complications. Two of these children eventually succumbed to the disease.

Children with small bowel disease had significantly poorer outcomes (p = 0.02) with five out of the six children who died having small intestinal involvement.

Children with intestinal involvement also had significantly longer hospital stays with the median (IQR) duration of hospital stay in those with small bowel disease of 10 (6–12) days compared with 5 (3–7) days in those with other sites (p = 0.0001).

Two different protocols for administering ATT were followed in India at the time of this study. **(7)** This included a directly observed anti tubercular therapy (DOTS) or a non-DOTS treatment which

Table 3
Surgery: findings & procedures.

Surgical Intervention (n=22)		
Operative Findings	Number	
Perforation Peritonitis	10	
Intestinal Obstruction	10	
	Adhesions (n=5)	Strictures (n=5)
Diagnostic	2	
Surgical Procedures		
Perforation Closure	1	
Resection Anastomosis	3	
Bypass	1	
Diversion Stomas	14	
Nothing Done	3	
Management Modalities		
Medical	Intervention Surgery, n (%)	Recurrence n (%)
DOTS (n=38)	10/38 (26.3)	1/35 (2.9)
Non-DOTS (n=37)	12/37 (32.4)	0/29 (0)

involved three monthly visits to the pediatric clinic for prescriptions. Under the DOTS strategy, anti-tuberculosis medications are swallowed by patients under the supervision of a health worker. Whereas in non-DOTS, drugs are taken by the patients on their own at home. In our cohort, 32 children (42.7%) received category 1 DOTS therapy and 6 children (8.0%) had category 2 DOTS therapy. Twenty-nine children (38.7%) received a five-drug non-DOTS regimen while 8 patients (10.7%) received a four-drug non-DOTS therapy [Appendix 1 (a,b,c); Table 3]. The median duration of treatment for both methods of administration was similar at around six months. Second line antibiotics were needed in 6 children and steroids were given to 3 children.

A large majority of our children (85%) were able to complete the prescribed therapy. The literacy levels and family income of caregivers did not affect the duration or completion of therapy. There was no significant difference in final outcomes of children who received DOTS vs non-DOTS treatment.

We looked at trends for DOTS vs Non-DOTS over time, and there was no trend for preferring either treatment in this cohort. When grouped per study period (2007–2010 vs 2011–2015 vs 2016–2021), there was no significant difference between DOTS vs non-DOTS ($p = 0.637$). Our numbers are small to further look at treatment subgroups.

Five children were lost to follow up.

Out of the 70 children with full follow-up data, 64 (91%) were considered cured while six children (9%) died eventually due to the disease process. The mean (±SD) age of the children who survived was significantly lower than those who died at 9.9 (4.6) years vs 15.2 (3.31) years, respectively ($p = 0.008$). In the six children who died, 83% had small intestinal involvement ($p = 0.02$). Also, two-thirds of children who died had surgery, but this did not reach statistical significance ($p = 0.62$) probably due to small numbers. Finally, the children who died were significantly older than the survivors ($p = 0.008$), with two of the six children aged 11–15 years and the other four aged 16–18 years.

In our cohort 67 children had isolated abdominal TB while eight had concomitant abdominal and pulmonary TB.

There were no significant differences between these two groups in terms of demography, abdominal signs and symptoms, BCG vaccination, medical treatment (DOTS vs non-DOTS; $p = 0.711$), need for surgery, complications, disease recurrence and final outcome (All p values > 0.05).

Statistically significant differences between these two groups were seen for weight loss ($p = 0.007$) with significantly higher weight loss in children with concomitant abdominal and pulmonary. Conversely the median (IQR) hospital stay was longer in children with isolated abdominal TB [6 (4–10) vs 4.5 (2.5–5.0); $p = 0.035$].

Twenty children also had other extra-abdominal sites of the disease.

6. Discussion

The sustainable development goals 3.3 and the WHO End TB strategy had planned to end TB by 2035. The world is unfortunately yet to cover more than half of the targets that have been set in combating TB [9].

Over 80% of TB cases occur in LMICs with 26% of the world's TB cases occurring in India of which 13% occur in children [9].

The abdomen is still an uncommon site for the presentation of TB, it is the 6th most frequent extra pulmonary site and is difficult to diagnose, which leads to delays in treatment [10].

Abdominal TB has been found to have an incidence of 1–3% among the total number of TB cases in children. Interestingly the incidence rate in our cohort was 7%, higher than the previously reported rates. This could potentially represent a rise in the burden of abdominal TB [11,12].

Studies done in India have shown a peak incidence in the second decade of life (11–15 years), similar to our cohort where the mean age was 10.1 years with the majority (34.7%) of our study patients being in the age group of 11–15 years. Studies done in South Africa, on the other hand, showed more prevalence in children below the age of 5 years [4,11,12].

TB is traditionally considered a vicious cycle of poverty, disease and suffering [13]. This impression has been changing and TB is no more the disease of the poor and our study did not find any evidence of lower income groups having a higher incidence of abdominal TB. Studies correlating education, family income and incidence of TB have had variable results [14]. Our study did not suggest that being poor or illiterate increases the chances of having an abdominal TB infection.

Abdominal tuberculosis is a challenging extrapulmonary site which is difficult to diagnose, since it can mimic a variety of conditions which without a clinical suspicion can remain undetected. Changes in immunological responses with age have a role to play with abdominal tuberculosis found to mostly affect children belonging to ages between 11 and 15 years, according to studies done in India and few other countries, whereas studies in South Africa had more children below the age of 5 years [10–13].

Abdominal tuberculosis may spread from other sites may be lymphatic or hematogenous. The bacilli can also enter the gastrointestinal system through the ingestion of unpasteurised milk or through the swallowing of coughed out sputum. The bacteria infect the mesenteric or intra-abdominal lymph nodes, where they can remain latent or cause disease spreading to involve the mesentery, omentum or peritoneal linings, intestines or solid viscera. Microscopically tubercles, composed of epithelioid cells, with peripheral zones of lymphocytes and Langhan's giant cells forming a granuloma with a central caseating necrosis are seen. Occasionally acid-fast bacilli can be seen within the granuloma [11].

Most cases present insidiously, with long standing non-specific symptoms with the mean duration was found to be longer if the sites involved were the lymph nodes or peritoneum. Intestinal involvement can present acutely, in the form of obstruction or perforation of an ulcer(s) [11,15].

According to literature intestinal involvement is less common with studies showing that abdominal lymph node and peritoneal disease are more common [12]. In our study group, although mesenteric lymph nodes were the most common site involved, 33.3% of the children had intestinal involvement, which is higher than reported in literature [12].

Though it was not statistically significant, more small intestine involvement was in adolescents in our cohort which may be suggestive of more adult type disease developing in this age group, however larger prospective studies are required to determine this hypothesis.

Other than its insidious presentation, approaching traditional non-formal practitioners, costs in seeking care and geographical and infrastructural barriers have been touted as reasons in delay of care [16].

Microbiological confirmation of abdominal TB can be a challenge with the bacterial load in extrapulmonary samples being very low and even DNA amplification tests have low positivity, though newer tests like Xpert® MTB/RIF Ultra may yield better sensitivity for tissue samples [12]. Wherever possible a histopathological confirmation is recommended.

Radiological investigations are safe and play an important role. A chest radiograph to look for features of pulmonary TB will help point towards abdominal TB. Abdominal radiographs are useful in cases of acute intestinal obstruction or perforation. Ultrasound and

CT scans have an important role to play as they are non-invasive tests and finding typical features like enlarged lymph nodes, mesenteric thickening, bowel wall thickening though not exclusive to TB however with clinical features, history of TB contact in high burden settings has been considered as evidence enough to start anti tuberculous therapy [11].

In order to reach the diagnosis, clinicians need to employ a combination of tests but in the real world often diagnosis is reached and treatment started on clinical suspicion or on exclusion of other disease processes. Along with clinical features, history of TB contact in high burden settings has often been considered as evidence enough to start ATT [12]. Often an improvement in symptoms after starting treatment is taken as confirmation of the diagnosis [17].

Abdominal TB in children unless drug resistant, usually responds well to medical therapy with six-month therapy [Appendix 1(a,b,c)] being found to be equivalent to nine-month therapy [17,18].

Cases which present with small bowel perforation or intestinal obstruction are more likely to progress to surgery [6]. Worryingly in our series more than 25% of the children required surgical management (with perforation being the indication in 59% of these patients), which is much higher than the 4–15% mark mentioned in other studies [10].

The general principles of a laparotomy are followed on those children where there is no option other than an operative intervention. Where possible we suggest adhesiolysis, perforation repair, primary resection anastomoses for a strictured segments with or without a formation of stoma. We have had a very low threshold for a stoma formation in these children which is reversed once medical therapy is over.

While this is a scenario that we dread, many a time we encounter a completely frozen abdomen and are not able to do any intervention. In such cases we attempt to leave a drain after a peritoneal lavage and hope that medical treatment will cause healing. In those children where we do an anastomosis or have caused iatrogenic injury to the bowel, we advise leaving a drain. Post operative complications were similar to those observed in other studies including fecal fistula, following anastomotic leaks which we try to convert to a controlled fistula [8].

Mortality due to abdominal TB in children has been reported to be around 4–12%. Mortality and morbidity have found to be significantly more in adolescents, children who have had the need for surgery and in those who had small bowel involvement. Post operative complications like surgical site infections and anastomotic leaks occur possibly due to the cachexic state of the patients and overall poor healing [2,6,19].

The COVID 19 pandemic has caused a setback in the progress achieved in access to TB care over the past decades by many years. TB mortality is expected to increase in future reports and there is also now a decreased reporting of cases [9].

Public health interventions for prevention of TB are not easily translatable to children [19]. Ideally all children with TB contact should have received isoniazid preventive therapy, however globally only 22% of household contacts below the age of five years receive it. In our cohort, 96% of our patients had BCG vaccination and still developed the disease. None of the children with positive contact history in our study had received any form of preventive therapy [9,20].

There has been a shift in Indian guidelines in 2020, towards drug sensitivity-directed therapy. Therefore, all children now have to be screened for rifampicin resistance through rapid nucleic acid amplification tests, at the outset and given therapy accordingly. This is to prevent the amplification of resistance to companion drugs if the patient was harbouring rifampicin resistance.

Fixed-dose combination tablets were introduced as daily therapy in 2016 as opposed to intermittent (alternate-day) therapy. This was done to simplify therapy, reduce the pill burden, improve adherence and prevent drug resistance due to missed doses. This change was implemented as per recommendations by the Standards of TB Care in India - WHO guidelines in 2014. Ethambutol was added to the continuation phase, to prevent monotherapy in case patients had Isoniazid resistance [21].

The recommended duration of treatment is six months. A recent Cochrane review article found six months of therapy to be equivalent to nine months for all types of abdominal tuberculosis.

Treatment duration may be extended beyond 6 months at the discretion of the treating clinician. Extending treatment for complications such as strictures and adhesions alone is not recommended [22,23].

Twenty two percent of Indian households faced catastrophic costs due to TB related expenditure in 2020 needs us to urgently increase efforts across the globe to fight this long prevalent disease [9]. A separate publication using a generalised linear model (GLM) has looked at variables which impact costs in this cohort. The results show that the average direct cost was $3095.00 (standard deviation [SD]: 3480.82) or 68,065.13 INR (SD: 76,539.69). The GLM results established that duration of treatment and surgical treatment were significantly associated with higher costs [24].

7. Conclusions

While much progress has been achieved in the understanding and management of TB, abdominal TB especially in children, still remains a dilemma. In all countries regardless of those being economically challenged, there is still no conclusive microbiological test. Clinicians continue to rely on clinical suspicion, and non-specific imaging to initiate ATT, response to which often confirms the diagnosis. Compliance to ATT determines the final outcome. An aspect of worry is the higher mortality seen in children with involvement of the small intestine, those undergoing surgery and in the adolescent age group.

8. Limitations and future implications

The limitations of our study include it being done at a single center, observational and predominantly retrospective study with small numbers in subgroup analyses and thus the need for larger multicentric prospective studies are necessary to validate our findings and develop effective preventive strategies, sensitive diagnostic tools, management guidelines and measures to improve surgical outcomes.

Regardless, this study highlights the presentation, treatment patterns and outcomes of abdominal TB in children, a disease which is often neglected in surgical literature.

Previous communication

Initial results presented at the annual congress of the British Association Of Pediatric Surgeons 2022.

Financial Support

This study was supported by a pump priming study grant from the NIHR Global Health Research Unit on Global Surgery, University of Birmingham, United Kingdom (Ref: DJAA. RGNP20248).

The funders had no role in the conduct of the study, analysis of the results or the writing of the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpedsurg.2024.04.006.

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