Tuberculosis in South and Central Africa

Understanding epidemiology - Improving diagnosis and management

Bélard, S.M.

Citation for published version (APA):
Chapter 10

Treatment of childhood tuberculosis: caregivers’ practices and perceptions in Cape Town, South Africa

*Paediatrics and International Child Health* 2015 Feb;35(1):24-8
ABSTRACT

Background: A child’s caregiver is key to the successful drug delivery and outcome of tuberculosis (TB) treatment. Understanding caregivers’ practices and perceptions is important in the management of childhood TB.

Objective: To investigate caregivers’ practices and perceptions regarding TB treatment of children.

Methods: A prospective, questionnaire-based study at Red Cross War Memorial Children’s Hospital, Cape Town, South Africa of caregivers of children receiving TB treatment. During the children’s follow-up visits at 1 (M1), 3 (M3) and 6 (M6) months after initiation of TB treatment, caregivers were interviewed face-to-face.

Results: Caregivers of 253 children being treated for TB were interviewed and 434 surveys were completed between May 2011 and April 2013. 168 (39%) questionnaires were completed at M1, 165 (39%) at M3 and 94 (22%) at M6. Median age of children was 41 months (IQR 20–81). TB drugs were generally obtained from clinics most commonly visited 1–3 times a week. Only 86/162 (53%) and 109/155 (70%) children had been weighed at the clinic at M1 and M3, respectively. Drugs were most commonly administered after meals (69%). Two-thirds of interviewees crushed, dissolved or mixed the tablets with beverages or food. Most (88%) respondents reported easy drug administration. Few adverse drug reactions were reported. In 54/427 (13%) of surveys, concomitant antiretroviral treatment was given, most commonly before TB medication.

Conclusion: Administration of TB drugs was regarded as easy, but differed substantially from recommended practice. Children were not weighed so that dosage could be adjusted, most caregivers crushed, dissolved or mixed the tablets with beverages or food, and administered medication after meals, all potentially contributing to sub-therapeutic drug levels.
INTRODUCTION

Children account for a considerable part of the world’s tuberculosis (TB) burden [1], and in South Africa (SA) it is estimated that they account for ~ 15% of the total TB caseload [2]. Recent advances in microbiological diagnosis have improved the ability to determine the paediatric TB caseload [3]. However, treatment has received less attention, despite the urgent need for new paediatric drugs, adequate fixed-dose combinations (FDC), paediatric drug formulations and child-friendly regimens. Adherence to TB treatment is a particular challenge in children. Administration of drugs requires a reliable caregiver; the dosage must be calculated according to bodyweight with dose adjustments required during treatment; drug formulations at required dosages are often unavailable and tablets need to be split. As small children cannot swallow tablets, they must be crushed or dissolved, leading to dosing inaccuracy and refusal of intake owing to the bitter taste. The caregiver bears a considerable responsibility for successful treatment outcome. Understanding caregivers’ perceptions and practices regarding administration of TB medication is important to improve management and reduce barriers to successful delivery of TB drugs to children [4]. The aim of this survey was to investigate caregivers’ practices and perceptions related to the treatment of children with TB in an area with a high prevalence of TB.

METHODS

A prospective questionnaire-based study was undertaken at the Red Cross War Memorial Children’s Hospital, Cape Town from May 2011 to April 2013. Consecutive caregivers of children (aged <15 years) with suspected pulmonary TB who were enrolled in a cohort study evaluating novel TB diagnostics [5] and who received treatment for TB were interviewed at the child’s follow-up visits at 1 (M1), 3 (M3) and/or 6 months (M6) after treatment initiation to assess practices and perceptions at different time-points during the course of treatment. Treatment was according to local guidelines and was overseen at the TB clinics. Local recommendations on TB include daily treatment, and dosage is according to weight categories. In the study area, directly observed therapy (DOT) is not commonly used in outpatient treatment; for children, the caregiver provides the daily treatment. The frequency of TB clinic visits, ranging from daily to monthly, is determined by the clinic according to the anticipated adherence of the patient or caregiver.

An identical standardised questionnaire was administered at M1, M3 and M6. It was administered face-to-face by the same research staff to the person accompanying
the child for the follow-up visits. If the interviewee did not speak English, the questionnaire was administered by research staff speaking the respondent’s language (Xhosa or Afrikaans). The questionnaire included questions about the interviewee’s relationship to the child, visits to the TB clinics, preparation of medication, treatment administration, treatment tolerance, and co-administration of other long-term medication. Questions were dichotomous, nominal and ordinal polytomous; some questions included options for open-ended answers. Additional demographic and clinical data were available from the study database.

**Statistical analysis**

For descriptive data analysis, ranges, ratios, medians and means were calculated. Comparisons were undertaken using the Wilcoxon rank-sum and x² tests; P < 0.05 was considered statistically significant. Questionnaires not matching the M1, M3 and M6 time-points and incomplete questionnaires were excluded from analyses.

The study was approved by the Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town. Written informed consent was obtained from the parents or legal guardians.

**RESULTS**

Caregivers of 253 children being treated for TB were interviewed and a total of 434 surveys were performed; seven (1.6%) were excluded from analyses (six owing to wrong survey time-points, one was incomplete). Of the remaining 427 surveys, 168 (39%) were performed at visit M1, 165 (39%) at visit M3, and 94 (22%) at visit M6. One, two and three surveys were done for 120 (48%), 92 (36%) and 41 (16%) children, respectively. The median age of the children was 40.8 months [interquartile range (IQR) 19.3–81.1]; 138 (32%) surveys were undertaken on children aged 0–24 months, 143 (33%) on children aged 25–60 months, and 102 (24%) on children aged 5–10 years.

For 365 (85%) surveys, the mother was the interviewee, followed by the father in 20 (5%), the aunt in 12 (3%), the grandmother in 10 (2%) and others in 20 (5%) these included sister, foster mother, grandfather, friend, nurse, caregiver). The interviewee was the main person administering TB medication consistently during the course of treatment in 155 (92%), 145 (88%) and 82 (87%) M1, M3, and M6 surveys, respectively.

The most common schedule for visiting the TB clinic was 1–3 times per week, followed by monthly, twice monthly and daily (Table 1). The frequency of TB clinic visits decreased throughout the course of treatment (Table 1). Obtaining repeat weight/s on the child during follow-up visit/s to the TB clinic was reported in 53–70% of surveys (Table 1). However, even amongst those who reported that children were
weighed at the clinic, treatment dosage adjustment according to bodyweight was reported in only 41/269 (15%) cases.

Amongst children attending TB clinics, 16/226 (7%) caregivers reported that the clinic had been out of stock of medicines on at least one occasion, and 4/226 (2%) had to leave the clinic without drugs as a consequence, resulting in no treatment for 1–7 days. Sixteen (4%) caregivers reported that the child had missed an appointment at the clinic, and in three cases alternative arrangements had been made by the clinic staff. TB medication was taken daily by 418 (98%); one respondent reported giving medicines on Monday to Friday.

Of 427 respondents, 296 (69%) stated that TB medication was administered at the same time each day, most commonly in the morning (52%), followed by the evening (8%) and afternoon (7%); a few respondents reported splitting drug administration in the day (Table 1). Most interviewees reported that TB medication was given after meals while around one-quarter gave the drugs before meals (Table 1). TB medication was crushed, dissolved and/or mixed with food in 69% while 30% reported that medication was swallowed or chewed (Table 1). The median age of children who chewed or swallowed TB medication was 96 months (IQR 61–136) while that of children for whom tablets were dissolved, crushed or mixed with food was 28 months (IQR 16–53, P < 0.0001).

Administration of TB medication was classified as ‘very easy’, ‘easy’ or ‘not difficult’ by 88% of interviewees and as ‘somewhat difficult’ or ‘very difficult’ by only 9% of respondents (Table 1). Of respondents who gave a ‘very easy’, ‘easy’ or ‘not difficult’ rating, 66% crushed, dissolved and/or mixed, and 33% chewed or swallowed the tablets. Of respondents who gave a ‘somewhat difficult’ or ‘very difficult’ rating, 95% crushed, dissolved and/or mixed tablets, while 5% chewed or swallowed them. Children for whom administration was rated ‘very easy’, ‘easy’ or ‘not difficult’ were significantly older than those for whom administration was difficult [median age (IQR) 45 (22–84) vs 24 (12–40) months, P < 0.0001].

Skipping medication was reported by 8%, 15% and 14% at M1, M3 and M6, respectively; there was no association with treatment length (P=0.144) (Table 1). Two respondents (one at M1 and one at M6) reported interruption of TB medication; interruption at M1 was owing to hepatitis [which retrospectively was either drug-related or owing to Epstein–Barr virus (EBV)], while that at M6 was the father’s decision. Interviewees who reported skipping TB medication specified that this occurred nearly every day in one case (2%), once or twice a week in 6 (12%), once or twice a month in 29 (56%), or only once or twice in 12 (23%), with a single dose omitted for only or up to 1 week of treatment interruption; four (8%) did not specify skipping.

An adverse drug reaction was reported in 25 (10%) children. Nausea and/or vomiting were the most common adverse reactions (16/253, 6%), followed by rash (6/253,
and constipation, hepatitis and fever (in one each, 0.5%). Twenty-eight per cent (119/427) reported administration of other regular medicine; in 54/427 (13%), this was antiretroviral treatment (ART). Twenty-eight (52%) caregivers gave ART before TB medication, 19 (35%) gave TB medication first, and seven (13%) reported no specific order, or did not know.

Table 1: TB treatment characteristics by month of treatment, n (%)  

<table>
<thead>
<tr>
<th>Survey Time Point</th>
<th>Month 1 n=168</th>
<th>Month 3 n=165</th>
<th>Month 6 n=94</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Follow-up schedule at clinics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>7 (4)</td>
<td>12 (7)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>1-3 times per week</td>
<td>88 (52)</td>
<td>75 (45)</td>
<td>36 (38)</td>
</tr>
<tr>
<td>Twice monthly</td>
<td>22 (13)</td>
<td>22 (13)</td>
<td>12 (13)</td>
</tr>
<tr>
<td>Monthly</td>
<td>29 (17)</td>
<td>47 (28)</td>
<td>34 (36)</td>
</tr>
<tr>
<td>Don’t know/ not yet been*/ other</td>
<td>22 (13)</td>
<td>9 (5)</td>
<td>9 (10)</td>
</tr>
<tr>
<td><strong>Weighing of child at clinic visit†</strong></td>
<td>86/162 (53%)</td>
<td>109/155 (70%)</td>
<td>60/91 (66)</td>
</tr>
<tr>
<td><strong>Time of TB drug administration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Same time each day</td>
<td>119 (71)</td>
<td>114 (69)</td>
<td>63 (67)</td>
</tr>
<tr>
<td>Morning</td>
<td>90 (54)</td>
<td>89 (54)</td>
<td>45 (48)</td>
</tr>
<tr>
<td>Evening</td>
<td>13 (8)</td>
<td>13 (8)</td>
<td>9 (10)</td>
</tr>
<tr>
<td>Afternoon</td>
<td>12 (7)</td>
<td>11 (7)</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Split administration</td>
<td>4 (2)</td>
<td>1 (&lt;1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>TB medication related to meals</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before meals</td>
<td>45 (27)</td>
<td>41 (25)</td>
<td>23 (24)</td>
</tr>
<tr>
<td>After meals</td>
<td>115 (68)</td>
<td>112 (68)</td>
<td>69 (73)</td>
</tr>
<tr>
<td>Either/with meals</td>
<td>4 (2)</td>
<td>7 (4)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Don’t know/blank</td>
<td>4 (2)</td>
<td>5 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Mode of TB drug administration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crushed, dissolved or mixed with food</td>
<td>118 (70)</td>
<td>112 (68)</td>
<td>63 (67)</td>
</tr>
<tr>
<td>Swallowed or chewed</td>
<td>48 (29)</td>
<td>51 (31)</td>
<td>29 (31)</td>
</tr>
<tr>
<td>Don’t know/blank</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td><strong>Ease of TB drug administration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very easy, easy or not difficult</td>
<td>141 (84)</td>
<td>152 (92)</td>
<td>83 (88)</td>
</tr>
<tr>
<td>Somewhat difficult or very difficult</td>
<td>21 (13)</td>
<td>11 (7)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Don’t know/blank</td>
<td>6 (4)</td>
<td>2 (1)</td>
<td>4 (4)</td>
</tr>
<tr>
<td><strong>Omitting to take TB intake</strong></td>
<td>14 (8)</td>
<td>25 (15)</td>
<td>13 (14)</td>
</tr>
</tbody>
</table>

* Seven surveys reported follow up at Red Cross Children’s Hospital, one follow up at Brooklyn Chest Hospital  
†Children with daily visits excluded
Of the 253 children, 202 (80%) completed 6 months of TB treatment, 34 (13%) were lost to follow-up and 17 (7%) needed TB treatment for more than 6 months. Longer TB treatment was indicated owing to defaulting treatment, drug-resistant TB or extra-pulmonary TB regimens in 11/17 children. Six children had persistent signs and symptoms after 6 months of TB treatment; of these, two swallowed and four crushed their TB medication, and five took it after meals.

**DISCUSSION**

Regular, correct administration of drugs is crucial in the treatment and outcome of TB disease in young children, and they are therefore highly dependent on their caregivers. In this survey, two-thirds of children were under 5 years of age, reflecting the age distribution of severe TB disease in children and highlighting the challenges of delivering effective TB treatment. To our knowledge, this is the first study to investigate caregivers’ practices and perceptions of providing treatment to children in South Africa, providing insight into local practices at different times during TB treatment.

Most respondents reported follow-up at TB clinics 1–3 times per week during the period of intensive treatment, with less frequent visits during the maintenance phase. This is consistent with South African guidelines to monitor children on TB treatment at least monthly during the intensive treatment [6]. Worryingly, only half of the interviewees reported that the child was weighed at the clinic, an important procedure to adapt treatment dosage to weight gain and thereby avoid under-dosage.

The reports of TB clinics being out of stock and the resulting treatment interruptions are also of concern as this may promote development of drug-resistant TB and compromise adherence.

More than two-thirds of caregivers administered TB medication after meals. This is contrary to the common TB treatment recommendations to take drugs on an empty stomach. A recent meta-analysis of studies assessing the impact of food on the two most important pharmacokinetic parameters of antituberculous treatment, Cmax (maximum concentration) and AUC (area under the curve) of both rifampicin (RMP) and isoniazid (INH), showed significantly reduced Cmax and AUC for INH and significantly reduced Cmax for RMP if taken with food [7]. Paediatric pharmacokinetic studies confirming good serum drug concentrations using the revised paediatric World Health Organization dosage recommendations were performed on fasting children [8,9]. Sub-therapeutic drug levels, which may result from interaction with food, were associated with unfavourable treatment outcome and acquired drug-resistance [10]. However, there is relatively little information on the effect of
food on drug levels in children [11]. The common local practice of administering paediatric TB medication with meals highlights the urgent need for studies to assess pharmacokinetic variables under ‘real world’ conditions, i.e. in non-fasting children. Given the currently limited knowledge, it appears reasonable to recommend that TB medication be administered on an empty stomach. Poor tolerability is unlikely as children usually tolerate TB drugs better than adults [12]; this is supported by the few adverse drug reactions reported in our survey.

The methods used to administer drugs may also affect therapeutic levels, particularly in children who are unable to swallow tablets. In this survey, more than two-thirds of caregivers prepared the drugs by crushing, dissolving and/or mixing with food or beverages. Among the drug formulations commonly used in the study area, only Rimactazid H Paed 60/60 tablets (rifampicin and isoniazid FDC) are to be chewed or dispersed in as little as 5 ml water while all other tablets are not dispersible, and the film-coated RITIBH tablets (rifampicin 150 mg, isoniazid 75 mg, pyrazinamide 400 mg, ethambutol 275 mg FDC) should not be broken. Besides alteration of drug activity and absorption by beverages and food, parts of crushed or dissolved tablets may not be swallowed. Crushed antiretroviral tablets (lopinavir/ritonavir) have resulted in reduced bioavailability of both drugs [13], and crushed INH tablets have been associated with treatment failure [14]. Although studies which assess drug pharmacokinetics in children use crushed tablets, they are prepared in a standardised way, using water for dissolving, and therefore may not represent ‘real world’ preparation practices.

Most children in this study responded well to TB treatment and were able to stop TB treatment after 6 months, suggesting that treatment had been effective. However, as children were not followed up after completion of TB treatment, long-term outcomes are unknown.

Almost 90% of respondents rated drug administration as easy; however, this was strongly associated with older age. Paediatric drug formulations (dosage format which is suitable for accurately, safely, effectively and adherently administering a medication to children of various ages [4]) are available for some diseases [15,16] but appropriate paediatric FDC for TB are not yet available. Paediatric three-in-one [RMP, INH, pyrazinamide (PZA)] and four-in-one [RMP, INH, PZA, ethambutol (EMB)] FDC with adequate dosing for different weight bands are urgently needed to simplify prescription and distribution and to avoid the need to split tablets.

Co-administration of TB and HIV drugs poses specific challenges because of potential drug interactions, adherence issues and toxicity. Guidelines for coadministration of TB and HIV drugs in children are lacking, as are data on the impact of administration time intervals on drug interactions. However, the practice of giving ART first reported by most caregivers is pragmatic as antiretrovirals may have a
bitter taste and cause vomiting, resulting in the need to re-administer ART and TB medication if TB medication had been given first.

A limitation of the study is that the survey was undertaken in a single hospital centre and included only children with disease sufficiently severe to necessitate hospital admission. A further limitation is that some interviewees were not the primary caregiver administering the TB medication. There might have been under-reporting by caregivers who missed treatment administrations or appointments. Further studies of caregivers of children with less severe illness and in other settings, and studies assessing long-term outcomes are needed.

The results raise several concerns, including failure to administer TB medication according to current guidelines, treatment interruptions, and lack of adjustment of drug doses by weight during the course of treatment. Operational issues such as drugs being out of stock and irregular weighing of paediatric patients should be addressed within the TB programme to optimise the potential efficacy of TB treatment in children.

**DISCLAIMER STATEMENTS**

Contributors WI, FB and HJZ contributed to the conception and design of the study. SB, WI, FB, LB, LM performed the interviews and collected data. SB, JM, LW and HJZ analyzed the data. SB, WI, LB, LW, MPG and HJZ wrote and revised the manuscript.

**FUNDING**

This study was funded by the National Institutes of Health, USA (R01HD058971), the National Research Foundation, South Africa and the Medical Research Council of South Africa Conflicts of interest. None of the authors has any conflict of interest to declare.

**ETHICS APPROVAL**

The study was approved by the Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town.
ACKNOWLEDGEMENT

We thank the caregivers and children for their participation. We thank the staff and management of Red Cross Childrens War Memorial Hospital for their support of the study.
REFERENCES


