554

Management of Latent Tuberculosis Infection in Child Contacts of Multi-Drug Resistant Tuberculosis

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ABSTRACT

Background: Few studies have described the treatment of latent tuberculosis infection (LTBI) due to multi drug resistant (MDR) tuberculosis (TB) in a pediatric population, and many of the medications used may have toxicities in this age group. After prolonged exposure to a teacher with cavitary MDR-TB, 31 children in a school developed LTBI. This retrospective study describes the treatment experience of these children.

Methods: Characteristics of the children as well as information about medications used, time on medications, adverse reactions and completion rates were collected on all children who started LTBI therapy.

Results: Of 118 tested child contacts of the teacher, 21 were TST positive on initial testing, and 10 converted their TST on retesting. Of these 31 children (mean age 9.6 years), most were students in the teacher's classroom (21/31). Only 3 children were foreign born and received BCG vaccine. Twenty-six students started therapy for MDR-LTBI with levofloxacin (LEVO) and pyrazinamide (PZA), however 12 (46%) required a change in therapy secondary to an adverse event. Of these 12, LEVO alone was used for all but one child who was placed on PZA and ethionamide (ETA). The most common adverse events included arthralgias and myalgias (46%), abdominal pain (31%), elevated hepatic enzymes (27%) and photosensitivity (27%). Overall, 100% of treated children experienced at least 1 adverse event, and 15 children (58%) completed at least 9 months of treatment. Ten children were unable to complete therapy due to adverse events and one child stopped treatment at the request of the family. These 11 children received a median of 113 days of therapy and their adverse reactions were transient, resolving completely. No student developed active TB during the treatment period or in follow up to date.

Conclusion: Therapy for LTBI in child contacts of MDR-TB is complicated by multiple adverse reactions however more than half of children in this cohort were able to complete therapy successfully.

INTRODUCTION

- Index case - 27 year old US born elementary school teacher with cough for 3 months and large left upper lobe cavity and infiltrate on chest x-ray
- History of travel to Mexico and the Philippines
- Sputum smear acid fast bacilli positive 4+, culture positive *M. tuberculosis,* resistant to isoniazid (INH), rifampin (RIF), ethambutol (EMB)
- The teacher exposed children at a private elementary school over a prolonged time period within her classroom, an adjoining classroom, and other group activities (circle time, homework club, carpool, and daycare).
- After consultation with local, state and national TB experts, treatment with levofloxacin (LEVO) and pyrazinamide (PZA) for 12 months was recommended for all children with positive TST results. However, completion of 9 months of medication was considered an adequate regimen.
- Children on treatment were evaluated by a physician monthly.
- All children with MDR-LTBI were medically evaluated every 3 months the first year, every 6 months the second year and had chest x-rays every 6 months for 24 months.

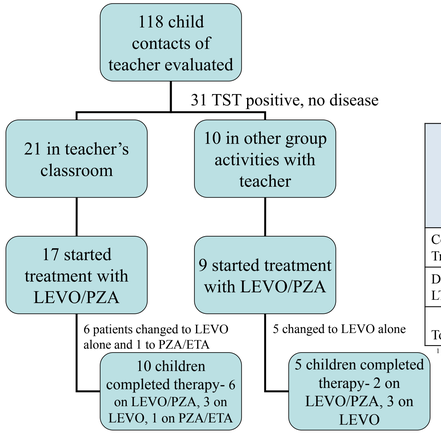


Table 2. MDR-LTBI Treatment Completion by Type of Regimen

	LEVO/PZA	Placed on Alternate Regimen[1] due to Intolerance of LEVO/PZA	Total
Completed MDR-LTBI Treatment (%)	8 (31)	7 (27)	15 (58)
Discontinued MDR-LTBI Treatment (%)	6 (23)	5 (19)	11 (42)
Total	14	12	26

[1] Alternate regimens: LEVO only (n=11) or PZA/ETA (n=1)

Table 3. Characteristics of Contacts Who Completed and Discontinued MDR-LTBI Treatment

Characteristic	Completed MDR-LTBI Treatment (n = 15)	Discontinued MDR-LTBI Treatment (n = 11)	Relative Risk (RR)	95% Confidence Interval	p-value
Teacher's classroom	10 (67)	7 (64)	1.06	0.52-2.15	1.00
Alternate treatment regimen	7 (47)	5 (45)	1.02	0.53-1.97	0.74
DOT at initiation of treatment	12 (80)	7 (64)	1.47	0.59-3.70	0.41
Median number of side effects ± SD	2 (± 1.5)	3 (± 1.6)			0.17

Table 4: Contacts with QFT and/or T- SPOT Results

Contact	US-born	BCG Vaccinated	Prior TST	Initial TST, induration in mm	Repeat TST, induration in mm	QFT Result	T-Spot Result
1	Yes	Unknown	Unknown	6	12	Positive	Negative
2	Yes	No	No	17	NA	Not done	Positive
3	Yes	No	Yes	16	NA	Not done	Positive
4	Yes	No	Yes	12	NA	Not done	Positive
5	Yes	No	No	10	25	Not done	Positive
6[1]	Yes	No	No	0	24	Not done	Positive
7	No	Yes	Unknown	0	14	Indeterminate	Negative
8	No	Yes	No	0	10	Negative	Not done

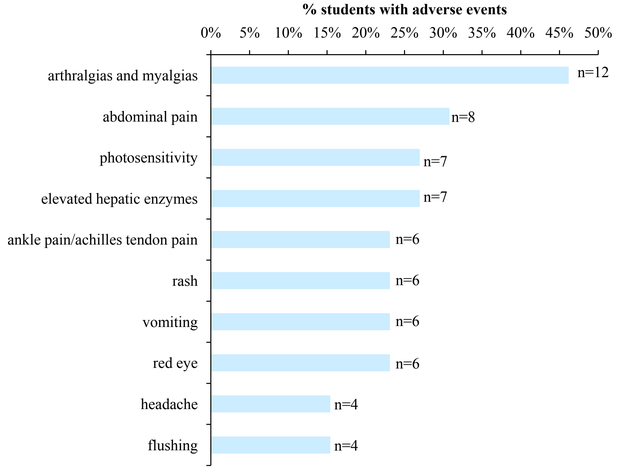
NA=Non-applicable
QFT= QuantiFERON®-TB Gold In-Tube, T-SPOT= T-SPOT®.TB
[1] had a series of T-SPOT tests done. Repeat T-SPOT results were discordant

Table 1. Demographic and Clinical Characteristics of Contacts with MDR-LTBI (n=31)

	No.
Gender	
Female	16
Age mean years (range)	9.6 (6-13)
Country of Birth	
US-born	28
Foreign-born	3
Race/Ethnicity	
White	29
BCG Vaccination	
Yes[1]	4
No[2]	24
Unknown	3
Prior TST (pre-exposure)	
Yes	13
No	15
Unknown	3
Started Treatment for MDR-LTBI	26
Directly Observed Therapy (DOT) at initiation of treatment	19
Self Administered Therapy (SAT) only	7
Completed Treatment for MDR-LTBI (%)	15 (58[3])
DOT at initiation of treatment (%)	12 (63[4])
SAT only (%)	3 (43[5])

[1] all foreign-born and 1 US-born contacts had a history of BCG vaccination
[2] 6 US-born contacts with unknown history of BCG vaccination and no opportunity for overseas BCG vaccination were included in the "NO" BCG category
[3] of contacts started on MDR-LTBI treatment
[4] of contacts started on MDR-LTBI treatment by DOT
[5] of contacts started on MDR-LTBI treatment by SAT

Ten Most Common Adverse Events in Contacts on MDR-LTBI Treatment (n = 26)



DISCUSSION

- Significant TB transmission can occur in a school setting.
- LEVO/PZA, PZA/ETA, and LEVO alone were used for treatment of MDR-LTBI in this group of children.
- Only 8 of 26 children (31%) were able to complete a regimen of LEVO/PZA, similar to experience in other patient cohorts. Adverse reactions to these medications were common, leading to discontinuation of therapy or change to an alternate regimen. LEVO alone was recommended as an acceptable alternate regimen *(per personal communication from Sundari Mase, MD re: a Chuuk MDR-TB outbreak and Gisela Schecter, MD re: a California high school MDR-TB exposure where in both situations a fluoroquinolone alone was used; no additional active TB cases have occurred among contacts so treated to date).*
- Careful monitoring is necessary when using these regimens for treatment of MDR-LTBI in children.
- All adverse events resolved upon discontinuation of therapy.
- Of the 26 children who started treatment for MDR-LTBI, 58% completed at least 9 months of treatment. Completion rates were higher in those children receiving DOT at initiation of treatment (63%) vs. those on SAT only (43%), p=0.41.
- No child developed active TB disease during the treatment period or follow-up to date (22 months since contact broken).
- Interferon gamma release assays (IGRA) results were available for a subset of children; in 2 children with positive TST and a history of BCG vaccination, IGRAs were helpful in ruling out LTBI.