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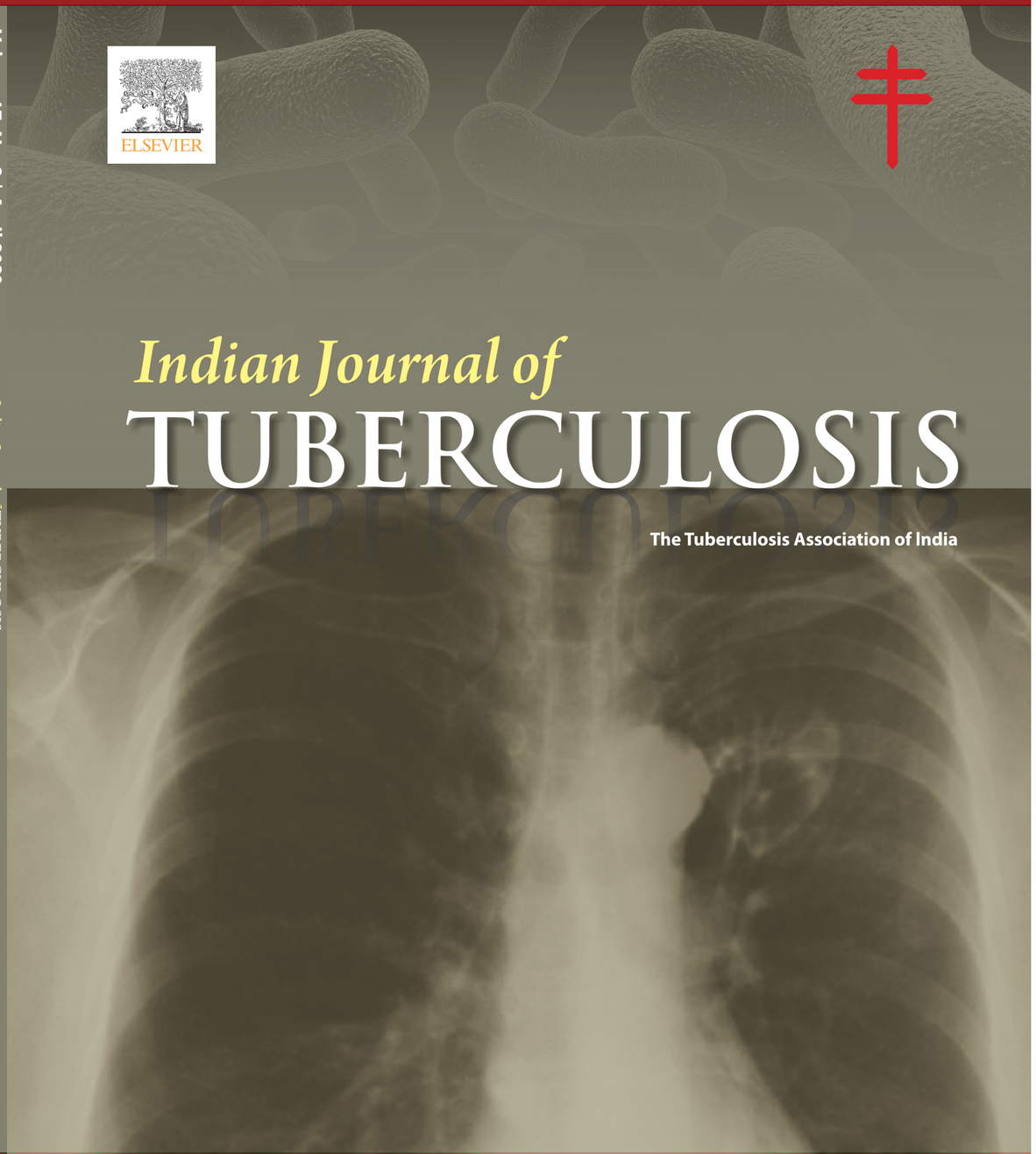

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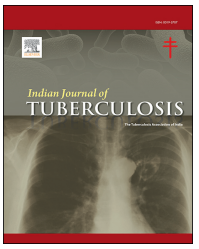

Editorial

COVID 19 and tuberculosis

On 31st December 2019, cases of pneumonia with unknown etiology were reported from Wuhan City of China to the WHO China Country Office. It marked the beginning of something terrifying that made the entire world to pause. Within a span of a week, i.e. by 7th January 2020, the causative agent of exponentially increasing pneumonia cases was identified as a new type of corona virus called SARS-CoV-2. Though the virus was found to be genetically related to the corona virus responsible for the SARS outbreak of 2003, the two virus are still different and on 11th February 2020 WHO gave the name COVID-19 (**CO**rona **VI**rus **D**iagnosed in 20**19)** to the disease caused by it.[1] In the blink of an eye, the novel corona virus disease became so wide spread that WHO announced it as a Pandemic on 11th March 2020 and caused 5,593,631 confirmed and 353,334 deaths being reported globally, based on information received from national authorities by 10:00 AM CEST, 28th May 2020.[2]

Till date the virus has infected a total of 158,333[3] persons in India among 3,362,136[4] samples tested so far (positivity 4.7%), with 4706[3] deaths so far as per ICMR & MoHFW, India as on 29th May 2020 9:00 AM IST. But, is it the only epidemic that is harbouring our world these days? Are we not forgetting the leading infectious cause of death in the world, Tuberculosis (TB). Meanwhile, all this COVID fiesta, TB is giving rise to an estimated 2.5 million new cases every year and causing 3.75 lakh death deaths, globally.[5] India alone accounts for 6.25 lakh new cases and nearly one lakh deaths annually (mortality rate 20%), leading the way here as well.[6] The picture gets worsened by the increasing number of drug resistant cases which in turn is taking the mortality rate to higher levels. Why are we so oblivious to one disease which is equally devastating and distinctive towards the other?

After China and Italy, world is looking over India in apprehension to win this war against the deadly virus. World is fighting this disease with its every might. What's not being done to curtail the devil? From strong politico-administrative commitment to inter-departmental (even inter-governmental at such times) coordination, from spate of advisories and public addresses to overflowing awareness drives on social media, from every possible preventive measure viz. educating about cough etiquettes, tracking down and isolating all suspected cases and contacts of confirmed cases and propagating awareness through every possible means, from prioritizing health care delivery services to stringent infection control measures at all levels, countrywide lockdown, unparalleled mobilization of resources, essential goods and management of human resources and what not. All is being planned and implemented in quickest possible time frame and guidelines being revised with updated data every short interval. That's impressive and imperative.

Can we compare our efforts to mitigate another epidemic prevailing in the country since decades? Celebrating yet another World TB day this 24th March 2020, did we even think of showing at least half of this commitment to save the lives lost due to lack of awareness or lack of required level commitment for the same. If we have to learn one thing from China then it can be the way it is curtailing its health issues one by one. First the population explosion, then nearly halved it TB prevalence in 20 years[7] by reducing the incidence of TB to a rate of 3–5% per year (1–2% per year global),[5] and now curbing the spread of most aggressive, agile and ambitious disease i.e. COVID-19 even. It is getting praises all over the world for its 'bold approach' necessitating strict social distancing, more than a month of city-wide lockdowns of the first affected city (Wuhan) and surrounding areas, extensive public monitoring of citizens, as well as various methods of punishment and rewards to encourage adherence to such measures.[8] When it has been established that single most effective contributing factor in this was "aggressive use of quarantines", similar strategies can go a long way to contain the spread of *mycobacterium tuberculosis* as well. With the ever growing multi drug resistant bacteria, it has become the need of the hour to start focusing on TB as well and take uncompromising relentless measures if to achieve the country's vision to eliminate TB by 2025. We can take learnings from everywhere if we really want to take it. The Chinese 10 year Infectious and Endemic Disease Control (IEDC) project 1991–2000 demonstrated that DOTS can be rapidly expanded provided that two critical elements are achieved viz. strong politico-administrative commitment and implementation of specific guidelines for TB control with rapid dissemination of generalized awareness, helping WHO to launch DOTS worldwide.[9]

Among the most commonly reported symptoms due to COVID-19 are fever, dry cough and shortness of breath whereas the most patients (80%) reported mild illness only

with elder age group people and those having underlying comorbidities at a higher risk. According to the limited information available, SARS-CoV-2 probably interferes with the host innate immune response, induces delayed type I IFN compromising early viral control, leading to cytokine storm eventually. In time of the epidemic, it was observed that without isolation measures, one infected person could have infected 2.5 people in 5 days which in turn could infect 406 people over 30 days but with proper isolation & containment measures the transmission rate could be decreased to as low as 1.05.[10] On the other hand, a person infected with TB has a lifetime risk of 5–15% of developing an active disease and an active TB patient could infect 10–15 people per year.[5] There is a saying in TB community: "TB anywhere is TB everywhere." Moreover, the list of vulnerable population for TB, which is way longer than that for COVID-19, includes immunocompromised individuals, People living with HIV, malnourished, diabetics, tobacco users, alcohol users, people other comorbid conditions, etc.

Two peculiar ways in which TB is showing us light at the end of the COVID-19 tunnel. Firstly, where we can see individuals with underlying disease like diabetes, hypertension and cardiovascular diseases, etc. are susceptible to CoVID-19 instead of young children with no evidences of developing severe cases as a result of highly effective innate immune response present.[10] Taking the facts, researchers are trying to establish a relation between BCG vaccinations providing some level of immunity from the disease, e.g. Netherlands and US have been more severely affected compared to countries with universal and long standing BCG policies. Countries implementing long standing BCG mass vaccination programs observed lesser number of infections and deaths recorded due to CoVID-19. India with world's BCG vaccine proved quite effective against SARS infection also in reducing the intensity. Several studies over the years have stated that BCG vaccines can accentuate a powerful immune response but does it render any protection from CoVID-19? Secondly, extensive experience of investigating close contacts with TB patients could be used as a learning tool to propose a strategy for SARS-CoV-2 screening and contact tracing in settings with low levels of community transmissions.[11] Tracing the three generations of contacts and offering timely testing if previous contact generation is detected positive, with sentinel testing of patients with respiratory symptoms among general population should be conducted to rapidly identify the onset of sustained community transmissions and thereby deploying the available resources effectively.[12]

TB has been in India since 3300 years and despite delivering positive information like such in times of emergency, couldn't muster the respect it deserves. However, the only thing that touches the notch of the charts for TB is stigma associated with it, which renders the situation more challenging with delayed diagnosis. Even after years of ongoing battle, an ardent political administrative commitment and rapid policy response, as incredible as it is for COVID-19, remains awry for TB. Despite specific guidelines from NTEP and Standards of TB Care in India, private sector health care providers still fail to implement them in their day to day practice which worsens the situation increasing out of pocket expenditure leading to decreased adherence giving rise to consequent drug resistant TB cases. People don't consider it necessary to follow basic simple cough etiquettes when it comes to TB, leave apart following isolation protocols.

As if the problems with TB control were not enough. The squall of coronavirus pandemic has rendered routine TB services to stand at the brink of diluted attention with diverted human resources. This may lead to a long term irreparable socio economic backlash. What we are fighting now, doesn't even have any specific treatment or any preventable vaccine in place yet. However, TB is a curable disease with antitubercular drugs and preventable with prompt diagnosis and early treatment of active TB cases, airborne infection control measures with proper cough etiquettes and treatment of latent TB infection. The preventive measures required for TB are not very much different from what is required for COVID-19.[13] The enthusiastic and mandatory use of masks in the wake of COVID-19 is adding a preventive benefit towards TB spread as well. On the contrary, increased lockdown implementation and strict quarantine measures have decreased the access to timely diagnosis and prompt treatment uptake as well, a reason to worry again. A little bit of strengthening and expanding the existing programmatic capacity, fully accountable private sector and a politico administrative support to TB control and program implementation can give speed to this battle against havoc TB continues to cause in our country.

It is understandable the fear and misery COVID-19 is causing among the masses and definitely the stratagem adopted were entailing. But we must not underestimate the much more sufferings and deaths TB is causing every day. Just because one disease surfaces up and scares us more should not be an excuse to loosen our grips on the one which has been the reason of the blues for millions in the country and worldwide as well. The situation today is like a doomsday scenario and these emanating emergencies demand to be confronted together through coordinated global health measures. Keeping in mind the most important lesson learnt: 'Prevention is the key to success', we must repurpose our tools to fight new pandemics while ensuring continuous health care service delivery to people seeking care from ongoing illnesses.

Conflicts of interest

None declared.

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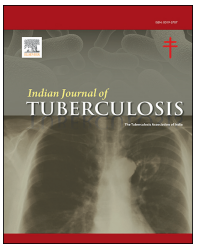

Original article

The risk of refeeding syndrome among severely malnourished tuberculosis patients in Chhattisgarh, India

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ABSTRACT

Background: A secondary care hospital in rural India serving a highly tuberculosis (TB) and malnutrition endemic region.

Objective: In this study conducted on patients with chronic protein energy malnutrition (PEM) and TB, we sought to compare nurse-estimated vs. smartphone photograph analytic methods for assessing caloric intake and determine the incidence of refeeding hypophosphatemia (RH) and refeeding syndrome (RFS) in patients with TB.

Methods: Inpatients were prospectively enrolled. Baseline demographic, comorbidity and preadmission caloric data were collected. Nurse estimated caloric intake was compared with digital "before and after" meal images. Serum phosphorus was measured on days 1, 3 and 7 post admission. Patients with RH underwent further evaluation for RFS-associated findings.

Results: 27 patients were enrolled. 85% were at risk of RFS by National Institute for Health and Care Excellence (NICE) criteria. Significant discrepancy (>700 calories) was noted between nurse-estimated caloric intake compared to digital images. RH was found in 37% (10/27). None developed clinical RFS.

Conclusions: Our study suggests more standardized methods of caloric intake are needed in resource-limited settings with high co-prevalence of PEM and TB. We noted that despite RH being common in inpatients with PEM+TB given high caloric diets, RFS was not detected.

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1. Introduction

Tuberculosis (TB) leads to 1.3 million deaths per year and significant morbidity for those afflicted. India contributes to 27% of the global burden of TB.[1] Tuberculosis is primarily a disease of poverty[2] and Protein Energy Malnutrition (PEM) is more prevalent than HIV as a risk factor for active TB in India accounting for >30% population attributable risk for active TB.[3,4] TB and PEM have a bidirectional relationship; the chronic inflammation, decreased appetite and increased metabolic demand[5,6] in active TB disease can worsen a patient's nutritional status.[4] TB patients with more prominent wasting have greater mortality,[3,4] and there is evidence that high calorie nutritional supplementation leads to improved outcomes.[7,8] Therefore, guidelines from the WHO and the Indian Ministry of Health recommend a high calorie diet, at least 40 kcal/kg/day,[9] which is 10–15 kcal/kg above recommendations for healthy adults.[10]

In resource-limited settings, accurate caloric intake measurement is limited by time and lack of standardization. Given the importance of caloric provision in TB recovery, a simple but effective way to measure intake is greatly needed.[11]

It is also known that in severely malnourished patients, reinitiation of feeding leads to risk of refeeding syndrome (RFS). This is a life-threatening constellation of symptoms that can affect patients who restart eating after a period of starvation. Risk factors include BMI <16 kg/m2 (or 18 kg/m2 with another risk factor), unintentional weight loss of >15% in the previous 3–6 months (or >10% with another risk factor), little or no nutritional intake for >10 days (>5 days with another risk factor), low baseline electrolytes, comorbidities such as alcohol abuse and cancer, or use of medicines such as insulin and diuretics that can cause electrolyte abnormalities. The pathophysiology is debated, but it is thought to be caused by fluid and electrolyte shifts from increased insulin and metabolic activity associated with metabolism of carbohydrates. RH is one of the hallmarks of RFS. A review of studies in anorexia patients showed an incidence of 14%.[12] Although the full-blown syndrome of RFS is more rare,[13] National Institute for Health and Care Excellence (NICE), UK, has established definitions for subjects at risk and recommend hypo-caloric feeding (5–10 kcal/kg/day) for all patients who meet a low BMI and low caloric intake criteria.[10] However, this recommendation is based on limited data.[14]

Though most patients with severe malnutrition and TB should be considered high risk for RFS by NICE criteria, to our knowledge, there is no data examining the incidence of RFS in this population. The Indian Ministry of Health guidelines offer no specific recommendations on management of patients at risk of RFS, but comment that hypo-caloric intake may be appropriate for some TB patients.[9] Further, there is emerging evidence from studies of patients with anorexia nervosa that hypo-caloric feeding may not prevent RFS[14–18] but rather leads to longer admission and poor weight gain, the 'underfeeding syndrome'[16,17,19,20] - thus questioning the evidence and benefit of hypo-caloric feeding in all patient groups.

Given the paucity of data on standardized caloric assessment of TB patients and incidence of RFS,[21,22] as well as the potential significant consequences of both under- and overfeeding in severely malnourished TB patients, we aimed to examine the incidence of RFS and associated caloric intake in these patients at Ganiyari Hospital in Chhattisgarh, India, a secondary care hospital in rural India with high prevalence of TB and malnutrition related to poverty.[3]

2. Study population and methods

2.1. Study design and setting

This was a prospective observational study conducted at Ganiyari hospital. Ganiyari hospital is a secondary care level center which caters to the population of rural Chhattisgarh, an area of over 1500 villages. There are higher rates of poverty, TB, and PEM than in the average Indian population, with 2/3 rds of women and 1/2 of men with active TB having a BMI <16 kg/m2.[3,23]

This study was approved by the Institutional Review Boards (IRB) of both Washington University in St Louis, MO, USA and Emmanuel Hospital Association in New Delhi, India. The trial was registered on ClinicalTrials.gov with identifier NCT03537170.

2.2. Patient population

This study was based in the inpatient TB unit of Jan Swasthya Sahyog's Ganiyari Hospital in the state of Chhattisgarh, India.

2.2.1. Inclusion criteria

All patients ≥18 years of age who were admitted to the TB unit during the study receiving enteral feeding who could provide informed consent.

Patients admitted to the hospital met one or more of the following criteria: 1) Inability to walk unsupported, 2) Extensive disease (two sites or more than a lobe in pulmonary TB) along with severe undernutrition (BMI below 16 kg/m2, 3) TB and diabetes requiring insulin titration, 4) TB and HIV requiring counselling and starting ART, 5) Severe anemia needing blood (hemoglobin below 7 mg/dl with hypoxia, below 5 mg/dl without hypoxia, 6) Supplemental oxygen requirement, 7) Suspected multi drug resistant TB requiring confirmation of the diagnosis and referral to DOTS plus center, and 8) any other medical or surgical admission indication for admission based on the treating clinician's judgement.

2.2.2. Exclusion criteria

Patients not meeting the above criteria or unable/refused to give consent.

2.3. Outcomes

Demographic and laboratory data. Patients were enrolled after appropriate informed consent on the day of admission. At baseline, demographic and clinical data were collected including BMI, home village, distance from the hospital, type of active TB, mode of TB diagnosis based on WHO criteria,[24] and risk of RFS. Baseline labs were recorded if available. These included serum potassium, phosphorus, HIV, fasting glucose, ALT, albumin, hemoglobin and creatinine.

Baseline dietary data. Baseline caloric intake was determined by a 3-day dietary recall method. This has previously been shown to be superior to 24 hour dietary recall alone.[25] This was recorded as average caloric intake per day. A food frequency questionnaire (FFQ), shown in Appendix 1, was administered and patients were asked how many times a day they eat, and how many times a week they eat. Type and frequency of carbohydrate and protein-rich foods were also recorded.

Caloric intake during admission. Starting on Day 1 of admission, patients were given standardized plates and caloric intake was recorded through digital photography (using a smartphone) before and after food consumption at every meal. Caloric count from these photos were determined from standard amounts charts. These standard amounts were determined by measurement of the capacity of serving utensils used by the hospital canteen as well as photographing predefined amounts of food, which are shown in Appendix 2. The method of using digital photography for caloric estimation was validated in a prior study which used a comparison to weighing of standardized, known-calorie count meals.[26] Calorie and protein contents were based on United States Department of Agriculture (USDA) standard food reference tables, and, when unavailable for certain foods, the website myfitnesspal.com. This website was chosen because of the availability of measures for difficult to find foods. Each item was cross-checked for validity by a registered dietician (PR). The methods used for calculating calorie and protein content of each individual food item are described in detail in Appendix 3, and final calorie and protein counts used are detailed in Appendix 4. Dietary charts done by the nurses as part of routine care were also recorded. Nurse estimation was done by visual estimation of food consumed based on amount of food on plate prior to and after meals. When an item listed on the nursing chart was not photographed, information obtained in chart was used. Photos were reviewed by 2 independent study physicians (PC and JG), and caloric estimates were recorded as an average of the two measurements.

Laboratory and clinical monitoring for RFS. On day 3, records were reviewed for phosphorus values, and, if low, follow-up studies including physical exam and lab studies (potassium, ECG), were done. This review was repeated at day 7. RH was defined as a decrease in serum phosphorus level of >0.5mg/dL from baseline or below 2.0 mg/dL. RFS was defined as RH along with a change in physical exam, electrolytes, or ECG.

2.4. *Statistical analysis*

The SPSS statistical package version 25 was used for data analysis.

3. Results

Baseline demographics, comorbidities, and caloric intake are listed in Tables 1–3. Median BMI was 15.2 and average % ideal body weight (%IBW) was 71.9%. Most patients (85%) were considered at risk of RFS. Although 60% of patients were anemic (average Hb 10.1 mg/dL), few had other comorbidities. Baseline food intake was poor in this underserved population, with average caloric intake of only 722 kcal per day on the day prior to admission. Food frequency data presented in Fig. 1 show poor protein consumption, with only 47% of patients consuming lentil (dal), egg, and meat >3 times per week. Rice was the most commonly consumed source of carbohydrate, and dal and rice were the most commonly consumed sources of protein.

Inpatient caloric intake was much higher with an average of 61.1 kcal/kg/day. A large proportion of calories were attributed to high carbohydrate intake (rice and potatoes), which was noted by photography and underestimated by nurse charts. No patients took a hypo caloric diet as per NICE guidelines for prevention of RFS (<10 kcal/kg/day). Protein intake was also high, with average intake 2.4 g/kg/day. Nurse

Table 1 – Baseline demographics

	N	Median	IQR
Age	27	35	24.5–55
Height	25	160	156–163
Weight	27	39.5	33.3–45.8
% IBW	25	71.9%	65.9–75.8
BMI	25	15.2 kg/m2	14.3–17.1
Distance from hospital (hours)	26	5.3 hrs	3.3–8.0

IBW: Ideal body weight, BMI: body-mass index.

Table 2 – Baseline demographics continued

Gender	Male	19 (70.4%)
	Female	8 (29.6%)
State	Chhattisgarh	18 (66.7%)
	Madhya Pradesh	9 (33.3%)
District	Annuppur (140 km/5hrs)	1 (3.7%)
	Bilaspur (20 km/0.75hrs)	11 (40.7%)
	Dindori (180 km/6hrs)	2 (7.4%)
	Jangjir Champa (70 km/2 hrs)	4 (14.8%)
	Kabeerdham (120 km/4 hrs)	1 (3.7%)
	Korba (120 km/4 hrs)	2 (7.4%)
	Shahdol (190 km/6hrs)	5 (18.5%)
	Umaria (290 km/12 hrs)	1 (3.7%)
Monthly income	Rs < 1000 (<$14)	5 (18.5%)
	Rs 1000–4999 ($14–69)	10 (37.0%)
	Rs > 5000 (>$69)	6 (22.2%)

Table 3 – Baseline comorbidities and risk for RFS

Pulmonary TB	21/27 (77.8%)
Extra pulmonary TB	7/27 (25.9%)
Hypoalbuminemia	5/22 (22.7%)
Transaminase elevation	2/25 (8.0%)
Anemia (Hb < 12)	20/27 (74.1%)
Diabetes (FBS >129 or known diagnosis)	6/26 (23.1%)
Hypophosphatemia day 1 (Phos <3.0)	3/24 (12.5%)
HIV	0/27 (0%)
Renal dysfunction (Cr > 1.0)	3/27 (11.1%)
Average baseline phosphorus	3.7 (2.1–6.3), std dev 0.9
At risk for RFS Yes	23 (85.2%)
No	2 (7.4%)

TB: tuberculosis, Hb: hemoglobin, Cr: creatinine, RFS: refeeding syndrome.

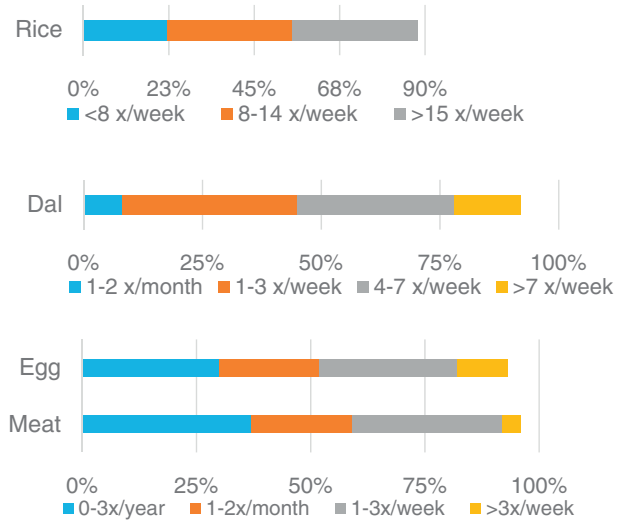

Fig. 1 – Food frequency data.

Table 4 – Incidence of RH, RFS, and inpatient caloric intake

	N (%)	Mean
Incidence of RH	10 (37%)	
# with TB	7 (26%)	
# with risk of RFS at baseline	9 (33%)	
# given phos supplements	3 (11%)	
Incidence of RFS	0 (0%)	
Average daily caloric intake		61.7 kcal/kg
Average daily protein intake		2.4 g/kg
Daily caloric intake of patients with RH		56.5 kcal/kg
Daily caloric intake of patients without RH		63.3 kcal/kg

RH: refeeding hypophosphatemia, TB: tuberculosis, RFS: refeeding syndrome.

estimates were lower than measurements obtained via photographic data, as shown in Fig. 2.

Baseline demographic variables and BMI distribution was similar among patients who developed RH compared to those who did not. Baseline phosphorus was slightly lower in those who did not develop RH (3.6 vs 4.1), Table 5. None of the patients with diabetes developed RH. These results are elaborated in Table 5.

4. Discussion

This study reports standardized caloric measurements in TB inpatients and the incidence of RH and RFS. Baseline caloric intake was low. Inpatient caloric intake was very high by a validated digital photography method, but standardized showed significant discrepancy from nurse visual estimation. RH was prevalent at 37%, but RFS was not detected. No patients had clinical symptoms that were consistent with RH or RFS. Although one patient was transferred to the ICU for volume overload, this was not attributed to refeeding as she received minimal food after admission. No major differences were detected in the RH vs no-RH groups, except that no diabetic patient developed RH but the number of patients with diabetes were small. Calorie measurement is important not only for optimal patient recovery but also for future studies on optimal intake for prevention of complications in TB patients. We implemented a method of measurement that is practical for resource-limited settings, and which can be adapted to extremely low resource settings.

To our knowledge, this is the first study reporting the risk of RFS in TB patients. The incidence of RH was similar to the incidence reported in the literature in critically ill patients, but higher than the average of 14% among studies in anorexia nervosa patients.[12] Published literature is predominantly available for anorexic and bariatric surgery patients.[12,16,18,21,27–29] There was no clinically significant RH or RFS detected among our study population even though most TB patients included in the study were at high risk of RFS.

This apparent lack of RFS in TB patients may be attributed to several factors. First, the higher basal metabolic rate among TB patients may lead to altered nutrient metabolism.[27,30] Phosphate may be consumed at a greater rate due to increased metabolic activity, but the previously described phenomenon of 'anabolic block' - a blunted anabolic response to protein consumption - may provide a protective effect against electrolyte and fluid shifts.[31] Second, our patient population, and much of the population that develops severe TB worldwide, is chronically malnourished, a characteristic which may provide some protection against RFS. It is unclear why this occurs, but it has been noted that patients that become acutely malnourished, such as those who have undergone bariatric surgery,[28] are at higher risk than chronically malnourished patients, such as alcoholics.[29]

Previous literature suggests that hypophosphatemia is associated with diabetes and insulin resistance.[32,33] Diabetic ketoacidosis patients commonly present with hypophosphatemia and require repletion. However, in our study population, none of the patients with diabetes developed hypophosphatemia. Adequately-powered studies may be required in the future to explain this unexpected finding.

Finally, the diet provided at Ganiyari hospital is high in phosphorus and this may be protective. Most patients consumed 500 mg phosphorus in the 2 cups of milk provided at breakfast. With beans provided at lunch and dinner, most patients likely exceeded the 700mg recommended daily intake. Although it is unknown whether phosphate supplementation reduces the risk of developing RFS, hypophosphatemia is directly responsible for clinical RFS symptoms such as hypoxia and decreased glycolysis, and early studies of patients who received parenteral nutrition without phosphorus showed poor outcomes.[34,35]

Our study had several limitations. Primarily, the small study size prevents us from making any strong conclusions about our findings. This was intended to be a pilot study with no sample size calculation, and the primary outcome may have been missed. Second, as the study was not blinded, the conduct of study procedures may have created increased awareness among staff about RFS, leading to a Hawthorne effect and increased rate of prophylactic supplementation.

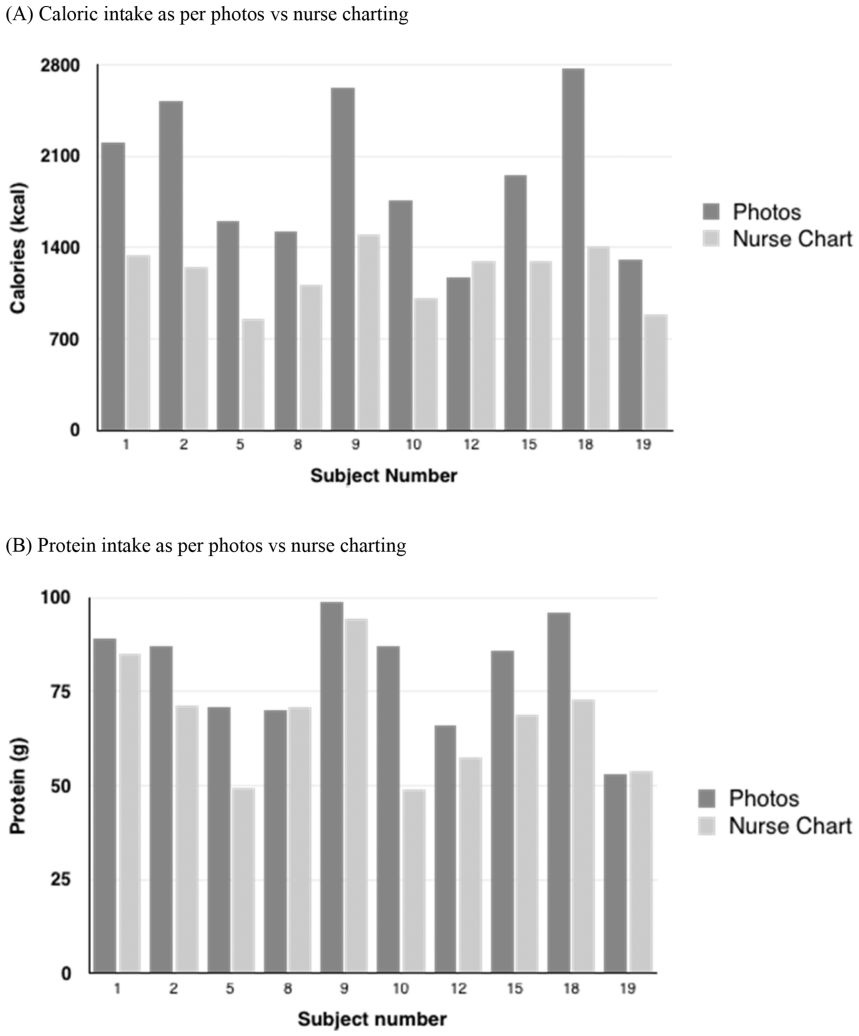

Fig. 2 – Caloric intake (A) and Protein intake (B) as per study data vs nurse charting.

Third, the questions about diet on the days prior to admission might have not accurately reflected the home situation in some patients as many patients were waiting in line for several days and may have reported their diet while eating in the hospital cafeteria. Fourth, phosphorus levels were not routinely performed in this hospital lab before this study, so the apparent 'protection' of a low phosphorus level at baseline may simply represent regression to the mean. Finally, given the observational nature of the study, all labs and ECGs were not available for all patients which may have limited the evaluation of our primary outcome.

Our results suggest that the risk of RFS in TB patients may be low by current NICE guidelines. Given the enormous number of TB patients worldwide who are currently considered at risk for RFS and their high mortality, a larger study on this topic is greatly needed to confirm these findings.

Table 5 – Characteristics of patients who developed RH vs those that did not

	RH (N = 8)	No RH (N = 19)
Age, mean (min–max)	37 yrs (19–70)	42 yrs (18–70)
Height	157 cm (144–167)	160 cm (148–170)
Male	6 (75%)	13 (68%)
Weight	38 kgs (28–51)	40 kgs (27–53)
% IBW	71% (61–88)	71% (54–87)
BMI (kg/m^2)		
<13.5	1 (13%)	3 (16%)
13.5–18.5	6 (75%)	13 (68%)
>18.5	1 (13%)	3 (16%)
Baseline phos	4.1 (3.3–5.6)	3.6 (2.1–6.3)
Diabetes	0%	6 (32%)

IBW: Ideal body weight, BMI: body-mass index, phos: phosphorous.

5. Conclusion

Our study suggests that more standardized methods of quantitative and qualitative caloric intake are needed in resource-limited setting with high co-prevalence of PEM and TB. Furthermore, we noted that despite RH being common in

inpatients with PEM+TB given high caloric diets, RFS was not detected (see Table 4).

Conflicts of interest

The authors have none to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijtb.2019.03.004.

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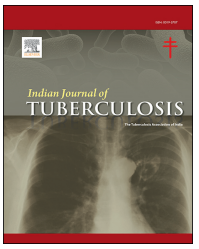

Original article

Incidental detection of disseminated peritoneal tuberculosis-varied presentation

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ABSTRACT

Background: Incidental peritoneal tuberculosis represents an uncommon variety of peritoneal tuberculosis and surgeons must be aware of this entity particularly in tuberculosis endemic zones.

Methods: We prospectively analysed cases of incidental peritoneal tuberculosis detected during surgery over a period of last six months.

Results: We herein describe three such cases of incidental peritoneal TB detected during surgical exploration for other reasons.

Conclusion: Diagnosis of disseminated peritoneal tuberculosis often remains a challenging task owing to its non specific clinical presentation and difficulty arises on seeing such a picture intraoperative and raises a question whether to proceed with the decided surgery or not. Frozen section can help in guiding further management but it is not definitive.

1. Introduction

Peritoneal tuberculosis is a rare entity and accounts for 0.1–0.7% of tuberculosis cases.[1] It can present with any of its three types. The wet type is the commonest one encountered in clinical practice and patient presents with abdominal distension due to loculated or free ascites. The fibrotic fixed type manifests as omental masses, matted bowel loops and mesentry. The dry plastic type is rare and is characterised by dense intra abdominal adhesions.[2,3] Tubercle bacilli gain entry into peritoneal cavity through infected mesenteric nodes, from tubercular salpingitis or haematogenously from a pulmonary foci.[4] We herein describe three cases of peritoneal TB detected incidentally during surgical exploration for other reasons. None of these cases had prior history of tuberculosis.

2. Cases

We prospectively analysed cases of peritoneal tuberculosis detected during surgery. We had three such cases over a period of six months from July 2018 to December 2018 at All India Institute of Medical Science, Rishikesh India. The clinical and operative details are described in Table 1.

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Table 1 – Case details of patients with incidental peritoneal tuberculosis.

Serial number	Age	Presenting complaints	Previous History of ATT	Surgery Planned	Intra operative findings	Frozen section	Final histopathology report
1	40	Abdominal distension and lump	No	Exploratory laparotomy with total hysterectomy	2litres ascites drained, Omental thickening with ilitary tubercles, Extensive intraperitonealmiliary tubercles, Fibroid uterus-20 weeks studded with tubercles, flimsy adhesions between bowel loops	No evidence of malignancy.Tuberculosis cannot be ruled out	Necrotising granulomatous inflammation consistent with TB,
2	32	Primary infertility	No	Diagnostic laparoscopy and proceed	100 ml ascetic fluid, frozen pelvis with inability to visualise uterus and tubes, extensivemiliary tubercles studded all over peritoneum, bowel and undersurface of liver,	Not done	Ascitic fluid ADA_40 U/L Peritoneal biopsy-TB
3	27	Primary infertility	No	Diagnostic laparoscopy	Uterus normal size, flimsy adhesions present over uterus, gut and omentum. Left tube was dilated with tubercles present over left tube giving tobacco pouch appearance.	Not done	Tuberculous granuloma

2.1. *Case 1*

40 years, Para 3 living 3 presented with abdominal distension since last 4 months. Her menstrual cycles were normal and there was no previous history of tuberculosis. Per abdomen examination revealed abdominal distension with suprapubic mass. Per vaginal findings suggested an 18 weeks fibroid uterus. Ultrasonography showed uterine fibroid (16 × 14cm) with degeneration with moderate ascites. Contrast enhanced computed tomography showed large uterine fibroid, retroperitoneal lymph nodes, gross intraperitoneal fluid with omental thickening. During surgery, she had 2litres ascites which was sent for cytological and biochemical study. Omentum was studded with tubercles and there was extensive intraperitoneal miliary tubercle. Uterus was 18–20 weeks with adhesion between bowel loops. Abdominal hysterectomy was done with multiple peritoneal biopsies Histopathology confirmed tuberculosis. Uterine serosa was also involved with numeroustuberculous granulomas (Figs. 1 and 2).

2.2. *Case 2*

32 years old lady presented with primary infertility for six years in gynaecology out patient department. Her menstrual cycles were regular and had documented ovulation in follicular study. Ultrasound revealed a right adnexal mass of 5 × 5 cm. On CECT, a right adnexal mass lesion of 6 cm was noted along with retroperitoneal lymphadenopathy. CA-125 was 29.3 U/l. She underwent diagnostic hysterolaparoscopy in view of adnexal mass. Intraoperatively, there was frozen pelvis with extensive miliary tubercles studded all over peritoneum, bowel and under surface of liver. There was minimal ascites which later on showed 75% lymphocytes with ADA level of 45U/L with negative acid fast bacilli. Peritoneal biopsy confirmed TB (Fig. 3).

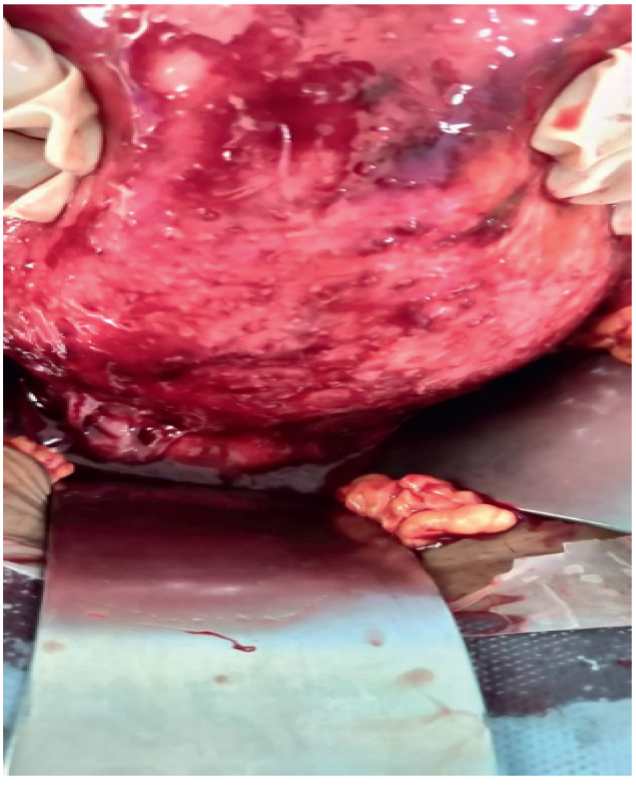

Fig. 1 – Posterior aspect of uterus with miliary seedlings (case 1).

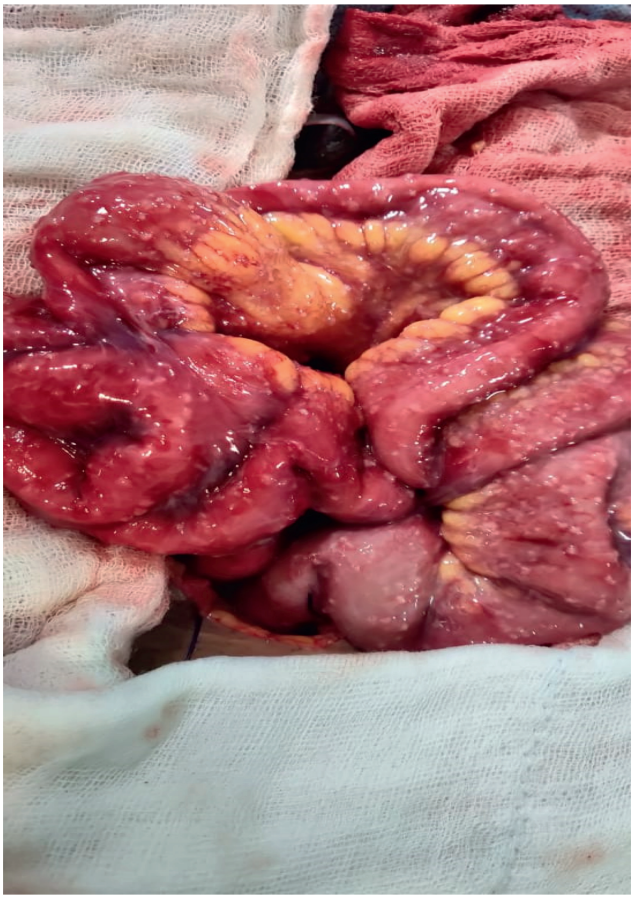

Fig. 2 – Extensive military seedlings over bowel (case 1).

2.3. *Case 3*

27 years nulligravida presented with primary infertility for seven years in gynaecology outpatient department. She had no menstrual irregularity. Hysterosalpingogram showed blocked right fallopian tube with patent left tube. Diagnostic laparoscopy revealed tobacco pouch appearance of left tube with studded tubercles. Right tube was partially visualised and it was embedded in adhesions. Tubercles were sent for biopsy (Fig. 4).

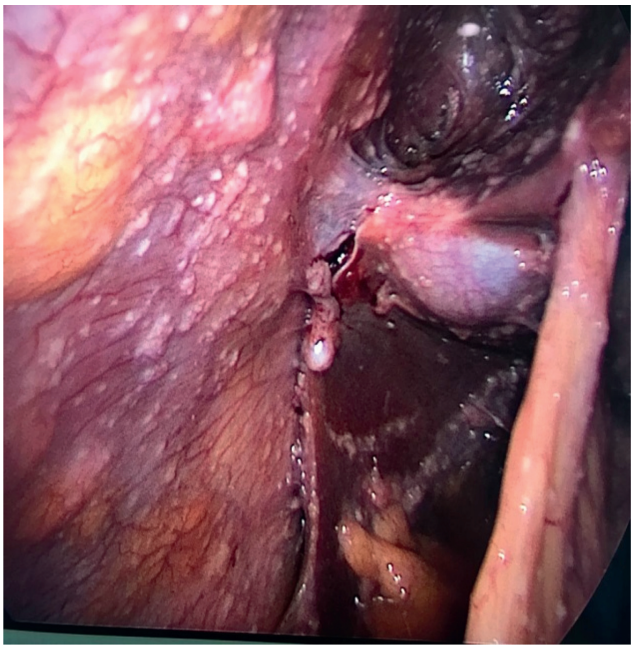

Fig. 3 – Multiple peritoneal tubercles (case 2).

3. Discussion

Peritoneal tuberculosis (TB) is a variety of extra pulmonary TB which involves both visceral and parietal peritoneum. Its diagnosis requires a high index of suspicion as it often remains asymptomatic and at times may be detected incidentally during surgery.

Krishnamurthy et al[5] described the entity of incidental peritoneal tuberculosis characterised by incidental detection of peritoneal tuberculosis (ascites or tubercles) in cases undergoing surgical exploration Such cases have no preoperative suspicion of abdominal TB and no active tubercular foci in body and surgery is done for other suspected pathology. Such a finding poses diagnostic dilemma and raises a question whether to proceed with original surgical plan or not. Both of our described cases were in fact incidental detection.

Preoperative diagnosis of peritoneal TB is often challenging owing to its non specific presentation. Surtiet al[6] described a case of peritoneal Tb mimicking ovarian malignancy. All of our cases had different presentations. In our first case, presence of ascites and omental thickening in the imaging should have raised a suspicion of associated peritoneal TB even though the ascitic fluid cytology was negative for acid fast bacilli. In the second case, it had mimicked adnexal mass. Histological finding of mycobacterium tuberculosis (MTB) remains gold standard for diagnosing peritoneal TB[7] but its slow growth in peritoneal fluid culture remains a major concern. Presence of adenosine deaminase (ADA) levels in ascitic fluid have 96% sensitivity and 98% specificity.[8,9] More than 40 units

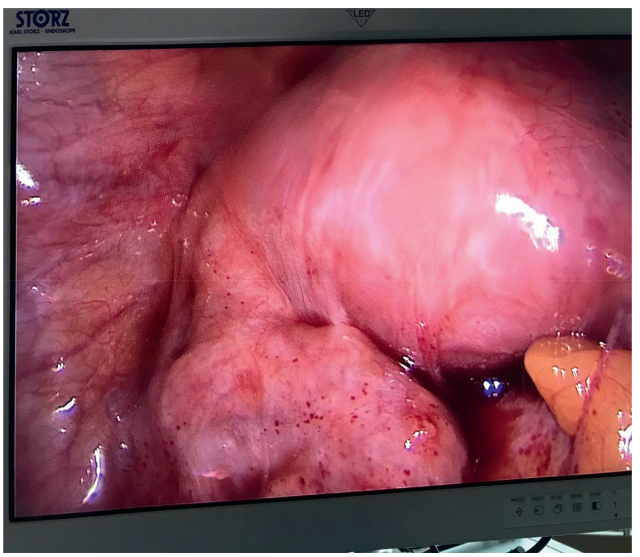

Fig. 4 – Dilated fallopian tube with tubercles. Uterus and tubes embedded in flimsy adhesions (Case 3).

per litre is indicative of tuberculosis. Imaging modalities like ultrasound and CT remains inconclusive. CA 125 can also be raised in such cases. Whenever there is a doubt for peritoneal TB, laparoscopy remains the best modality with biopsy taken from suspicious nodules or tubercles.[8]

Safarporet al[10] evaluated the role of laparoscopy in peritoneal TB. Presence of small whitish tubercles studded all over the peritoneal surfaces, thickened omentum and inflammatory adhesions on visceral and parietal surfaces is characteristic of peritoneal TB.

Primary peritoneal carcinomatosis remains one of the differential diagnosis whenever intraoperative picture shows multiple peritoneal nodules with no apparent ovarian mass, as was in our first case. Frozen section can help in guiding further management but it is not definitive. Kocet al[11] in their study concluded that majority of cases of peritoneal Tb can be diagnosed intraoperatively through the use of frozen section in association with clinical features thereby avoiding further extensive surgery. Even though frozen section ruled out malignancy in our first case, intraoperative findings were suggestive of peritoneal tuberculosis. In view of large uterine fibroid, we decided to proceed with abdominal hysterectomy. Genital TB remains one of the most important causes of infertility especially in developing countries. Endometrial samplings in all of our cases were negative for tuberculosis. Intraoperative, in the second case, there was frozen pelvis with multiple peritoneal tubercles with mild ascites. There remains a risk of port site tuberculosis in cases of peritoneal tuberculosis.[12] We decided to abandon the procedure and took peritoneal biopsies and aspirated ascetic fluid for Tuberculosis testing. Biopsy showed granulomatous inflammation suggestive of TB. ADA in ascitic fluid was high with a strong suspect of TB. Third case had military tubercles over fallopian tubes with pelvic adhesions. Till date, none of our cases developed port site or incision site TB probably due to start of anti tubercular drugs in post operative period.

4. Conclusion

Diagnosis of disseminated peritoneal tuberculosis often remains a challenging task owing to its non specific clinical presentation. Difficulty arises when such a picture is seen intraoperative and raises a question whether to proceed with the decided surgery or not. In spite of the risk of port site or incision site metastasis, decision to proceed with further surgery should be based on the risk benefit to the patient.

Conflicts of interest

The authors have none to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijtb.2019.06.002.

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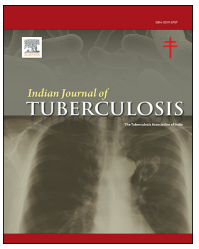

Original article

Functional exercise capacity in young survivors of acute respiratory distress syndrome

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ABSTRACT

Background: As survival rates improve among patients with the acute respiratory distress syndrome, there is a growing need to understand the long-term effects of pathology, treatment and complications in ARDS survivors.
Objectives: To study and evaluate functional exercise capacity in young survivors of acute respiratory distress syndrome.
Methods: A total 35 ARDS survivors with age between 20 and 40 years were selected in ARDS survivor group; which had history of hospitalization for ARDS in last 6 months. Similarly 35 age-sexes matched normal individuals also selected in control group. Each subject assessed for functional exercise capacity with 6 minute walk test and 15 step oximetry test.
Results: After analysing the data the results showed significant decline functional exercise capacity. It is found that, 69% patients walked distance between 301 and 450m and 28% patients walked more than 451m and remaining 3% patients walked less than 300 m distance in 6 minute walk test. 69% patients done exercise in 45–65 seconds, 28% patients done exercise in 21–45 seconds, 3% patients took time more than 66 seconds in 15 step oximetry test.
Conclusion: Young survivors of the acute respiratory distress syndrome have reduced functional exercise capacity 6 months after discharge from the intensive care unit.

1. Introduction

Acute Respiratory Distress Syndrome (ARDS) is serious lung disorder that develops suddenly as a result of severe damage either to the lungs or elsewhere in the body. ARDS is common cause of Incentive Care Unit admissions in Hospitalsall over world. The types of acute lung injury that leads to ARDS are very diverse. Bacterial sepsis is the most important cause of ARDS in hospitalised patients. Pneumonia, H1N1, burns, gastric aspiration are also other common causes of ARDS. It can occur in those who are critically ill who have significant injuries.

The symptoms of ARDS usually begin 24–48 hours after the injury or disease that causes condition. Severe shortness of breath, wheezing, confusion or unconsciousness are common

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symptoms of Acute Respiratory Distress Syndrome. Low oxygen levels in body, fever, coughing, high carbon dioxide levels in blood, muscle weakness are also sign of Acute Respiratory Distress Syndrome.[1]

Acute respiratory distress syndrome (ARDS) is an inflammatory condition of acute respiratory failure with various causes that is often treated by mechanical ventilation (MV) to provide respiratory support. Almost all patients of ARDS are treated with mechanical ventilation.Tracheal intubation should done to keep airway open.Treatment of Acute Respiratory Distress Syndrome requires supportive care, including positive pressure ventilation or continuous positive airway pressure (CPAP). Oxygen therapy provides extra oxygen to the lungs of patients with breathing problems.[2]

Patients who survive the Acute Respiratory Distress Syndrome are left with pulmonary complications. Respiratory system is mainly affected in survivors. Patients who survive are at risk at physical and neuropsychological complications because of their long stay in intensive care unit. Health related quality of life is also diminished. There are many other unknown complications that occur after surviving Acute Respiratory Distress Syndrome.[3]

Several investigators have evaluated morbidity among survivors of Acute Respiratory Distress Syndrome using pulmonary-function tests, neuropsychological and cognitive assessments, and quality-of-life measures and most have indicated that there is morbidity after discharge from the ICU.[4] But there is lack of study on functional deficits of Acute Respiratory Distress Syndrome. Our study will focus on testing Functional Exercise Capacity in young survivors of ARDS.

The past two decades have seen notable progress in ARDS management. A more accurate definition has been proposed and major progress has been achieved in understanding the ARDS pathophysiology and ventilator-induced lung injury.[5] In addition, protective-lung mechanical ventilation and adjuvant therapies such as prone positioning and neuromuscular blockers have contributed to improvements in overall ARDS mortality.[5]Survival rates among patients with the Acute Respiratory Distress Syndrome is constantly improving, there is a growing need to understand the long-term effects of Acute Respiratory Distress Syndrome and its treatment and complications.[6]

Several tests are available for the evaluation of functional capacity in patients with ARDS and lung diseases. These include the cardiopulmonary exercise test, the 6 minute walk and the 15 step exercise oximetry test. The CPXT is considered the gold standard but it is more expensive than other tests that were proven useful for clinical purposes. There is less information in the literature on a functional exercise capacity in survivors of Acute Respiratory Distress Syndrome. Previous studies focused on morbidity after acute respiratory distress syndrome. This study aims on to find out functional exercise capacity in young survivors of Acute Respiratory Distress Syndrome. It will help in improvement in treatment and rehabilitation programme. Also helpful to find out work related problems in young survivors and improving quality of life.

2. Methods

2.1. Study design

It was an analytical study.

2.2. Selection criteria

The details of ARDS survivors were taken medical record unit of Krishna hospital and medical research centre and 35 patients who survived with acute respiratory distress syndrome, were selected in study group. The inclusion criterion for study group was 1. All patients had a history of hospitalization in the last 6 months. 2. Their ages ranged from 20 to 40 years old. All patients were young survivors of Acute Respiratory Distress syndrome. Patients with history of other lung diseases like COPD, pulmonary tuberculosis, etc., other lung surgeries and organophosphate poisoning were excluded. Patients with occupational exposure to pulmonary irritants were also excluded. In control group, 35 healthy young (20–40 years old) subjects were selected. Written informed consent was taken from the subjects those willing to participate. The detailed outcome assessment was done. Karad.

2.3. Study procedure

After getting permission from protocol and ethics committee, Information of Young survived patients of Acute Respiratory Distress Syndrome was collected from Medical record unit of Krishna Institute of Medical Sciences. Subjects were selected according to inclusion and exclusion criteria as given above. All patients were screened for Acute Respiratory Distress Syndrome. In this Study age-sex matched subjects 35 subjects were included in both study and control group. A detailed history was taken from patients before assessment (Table 1). Patients were selected according to selection criteria. The functional exercise capacity assessment was carried out in presence of Medical officer and medical emergency staff. 6 minute walk test was taken firstly.6 minute walk test was performed along a measured indoor corridor in our institute. Participants were encouraged to cover as much distance as

Table 1 – Demographic Variables of study group.

Demographic variables	Group	Total subjects
Age	21–25	0%
	25–30	14%
	31–35	34%
	36–40	51%
Sex	Male	66%
	Female	34%
BMI	Underweight	0%
	Normal	57%
	Overweight	43%
Systemic Disease	Hypertension	9%
	Diabetes mellitus	6%
Smoking	Male	20%
Drug Therapy	Oseltamivir (Tamiflu)	100%

possible. Walk distance was measured and noted. After rest time, 15 step oximetry test was taken. A finger oximeter with continuous online recording of heart rate and oxygen saturation was connected to each patient. A step measuring 25 × 25 × 20 cm was used. Patients were asked to climb up and down the step 15 times as fast as they could (without any fixed pacing).Then patients were asked to climb up and down as fast as they could on given step for 15 times. After that oxygen saturation difference between pre and post exercise was measured with total time taken for exercise.

The motive of the study was thoroughly explained to the subjects. Informed consent from each subject was taken.6 minute walk test and 15 step oximetry tests were taken as outcome measure. The data from both the outcome measures was collected. After examining all the subjects the statistical analysis was done.

3. Results

All 35 patients who survived from Acute Respiratory Distress Syndrome completed the 6 minute walk test and 15 step oximetry tests. Results of study functional exercise capacity in young survivors of Acute Respiratory Distress Syndrome shows following results.

1) 6 min walk test distance(m) results of study group (Table 2):
2) 6 minute walk test distance (m) results of control group (Table 3):

Our result shows that, 83% from study group and 28% from control group walk more than 451 m distance. 69% and 17% walk between 301 and 450 m from study and control group respectively. Only 3% subjects walk less than 301 m from study group and none of subjects of control group walk less than 301m.

3) 15 step oximetry test: Exercise time in 15 step oximetry test results of study group (Table 4):
4) 15 step oximetry test: Exercise time in 15 step oximetry test results of study group (Table 5):

Our results show that, in study group, 28% subjects complete their exercise of 15 step oximetry test in 21–45 seconds. 69% subjects completed the exercise in about 45–65 seconds, 3% subjects took time between 66 and 80 seconds to complete the exercise.

In control group, 77% subjects complete their exercise of 15 step oximetry test in 21–45 seconds. 23% subjects completed the exercise in about 45–65 seconds and no subject took time between 66 and 80 seconds to complete the exercise.

5) SaO2 difference of Study group (Table 6)

Table 2 – 6 minute walk test results of Study group.

Distance	>451	301–450	<300
Subjects	28%	69%	3%

Table 3 – 6 minute walk test results of Control group.

Distance	>451	301–450	<300
Subjects	83%	17%	0%

Table 4 – Exercise time in 15 step oximetry test results of Study group.

Exercise time	Mild 21-45	Moderate 45-65	Severe 66-80
Subjects	28%	69%	3%

Table 5 – Exercise time in 15 step oximetry test results of Control group.

Exercise time	Mild 21-45	Moderate 45 -65	Severe 66-80
Subjects	77%	23%	0%

6) SaO2 difference in oximetry test results of Control group (Table 7):

SaO2 difference in oximetry test shows following functional group shows following results, In functional group, 57% subjects shows difference between 0.5 and 1.5 and 23% subjects shows Sa02 difference between 1.51 and 3.0. In control group, Only 20% subjects shows between 0.5 and 1.5 and remaining subjects shows no difference.

4. Discussion

To the best of our knowledge this was the first of its kind study conducted on rural Indian ARDS survivors. This study was conducted to assess the functional exercise capacity in young survivors of acute respiratory distress syndrome after 6 months of discharge from intensive care unit. Acute Respiratory Distress Syndrome is a common cause of intensive care unit admissions and mechanical ventilation whose symptoms are shortness of breath, wheezing, confusion or unconsciousness.Pneumonia, H1N1, burns, gastric aspiration and bacterial sepsis are causes of ARDS. ARDS is resulting in pulmonary infiltrates, refractory arterial hypoxia and stiff lungs.[7] Patients who survive are at risk at physical complications and diminished health related quality of life because of their long stay in intensive care unit (ICU).

This study is designed to identify the functional exercise capacity to help further research and widen the horizon of importance in physical activity in long term healthy survivorship in ARDS. Study was conducted with 35 patients who diagnosed with Acute Respiratory Distress Syndrome and 35 normal healthy subjects.The motive of the study was thoroughly explained to the subjects. Informed consent from each

Table 6 – SaO2 difference in oximetry test results of Study group.

SaO2	0.5–1.5	1.51–3.0	>3.1
Subjects	57%	23%	0%

Table 7 – SaO2 difference in oximetry test results of Control group.			
SaO2	0.5–1.5	1.51–3.0	>3.1
Subjects	20%	0%	0%

subject was taken. Patients was assessed with 6 min walk test firstly and then after some rest time patient was assessed with 15 step oximetry test.

After analysing the data, it is found that functional exercise capacity in survivors of Acute Respiratory Distress Syndrome is decreased after 6 months of discharge from intensive care unit as compared to normal healthy individual. Our study results suggest that reduced functional exercise capacity is caused by pulmonary disease and long stay in hospital. Health related quality of life also diminished in survived patients.

Earlier studies showed varied results on Respiratory, musculoskeletal and neurological system. These studies were conducted in western countries. Margurate Heritage and colleagues found that survivors of the acute respiratory distress syndrome persistent functional limitation one year after discharged from Intensive Care Unit, largely as muscle weakness and, to a lesser extent, to entrapment neuropathy, heterotopic ossification and intrinsic pulmonary morbidity.[8] Another study by Zhi YongWangand his colleagues found many of the survivors reported various degrees of muscle weakness and fatigue after 1 year of discharged from hospital.[9]

Study of James Orme Jr and his co-workers confirms that ARDS survivors have significant pulmonary impairment. Survivors also have reduced pulmonary function and impaired quality of life.[10] Ghio and colleagues surveyed 25 patients who survived ARDS, study reported that 50%patients reported respiratory complaints, including dyspnoea, cough and dyspnoea and diminished quality of life.[11]

In summary, our study shows that, functional exercise capacity is reduced in young survivors of Acute Respiratory Distress Syndrome after 6 months of discharge from intensive care unit. But we still don't know about full recovery of patients from illness or how much time they will take for full recovery. Our data demonstrate need of detailed study of the nature of pulmonary impairment in Acute Respiratory Distress Syndrome. The Study with investigation modalities like High resolution CT scan will help in detailed study of lung structural changes, long term effects and treatment of Acute Respiratory Distress Syndrome.

5. Conclusion

Young survivors of the acute respiratory distress syndrome have reduced functional exercise capacity 6 months after discharge from the intensive care unit.

Conflicts of interest

The authors have none to declare.

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Appendix A. Supplementary data

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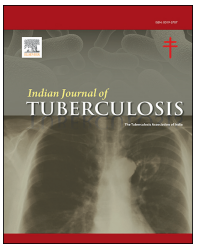

Original article

Prognostic value of some serum protein fractions as Early Index of Clinical Recovery in Pulmonary Tuberculosis subjects

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ABSTRACT

Background: Malnutrition is an important risk factor for pulmonary tuberculosis and can result to adverse treatment outcomes.

Aim: This was a cross-sectional study designed to assess prognostic value of some serum protein fractions in pulmonary tuberculosis (PTB) subjects at Oron, Akwa Ibom State, Nigeria. Thirty (30) TB subjects on Anti-tuberculosis therapy, thirty (30) drug naive TB subjects and thirty (30) apparently healthy control subjects aged 21–52 (35 ± 16) years were conveniently recruited.

Methods: Total protein and albumin were measured colourimetrically, Albumin-globulin ratio was calculated while demographic data was obtained using questionnaire.

Results: BMI (kg/m^2), Albumin (g/dl) and AGR were significantly lower in TB subjects with or without ATT when compared with control subjects ($p < 0.000$ respectively), but higher in PTB subjects on ATT when compared with drug naive PTB subjects ($p = 0.000$ respectively). Serum Total protein (g/dl) level in PTB subjects with or without ATT was significantly higher when compared with controls ($p = 0.004$) while globulin (g/dl) level was lower in PTB subjects on ATT when compared with drug naive PTB subjects ($p = 0.000$).

Conclusion: Decreased BMI in TB subjects signifies reduction in muscle mass and wasting precipitated by PTB infection, while depleted albumin and AGR suggests high degree of malnutrition. Increased albumin and AGR in PTB subjects on ATT suggests improvement with ATT. Assessment of serum albumin and AGR may serve as affordable and early index of clinical recovery in PTB subjects especially in resource limited settings, and may be more reliable than the traditionally used BMI.

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1. Introduction

Despite the recent improvement in the availability of anti-tuberculosis therapy, tuberculosis remains a major cause of morbidity and mortality worldwide.[1] There has been a report of resurgence of TB worldwide with majority of the cases in developing countries including Nigeria.[2] HIV-1 epidemic and malnutrition are major predisposing factors.[2,3] Others risk factors include smoking, diets and chronic liver disease.[4]

Previous report has shown that tuberculosis and malnutrition are synergistically related.[2] Specifically, tuberculosis may cause malnutrition through increased metabolic demands and decreased nutrient intake, while nutritional deficiencies may worsen the disease or delay recovery by inhibiting important immune functions.[2] One of the classic signs of tuberculosis is weight loss,[5] suggesting that underweight (BMI< 18.5) increases the risk of TB while higher BMI on the other hand decreases the risk.[6] Report has shown that there are changes in levels of serum proteins fractions in response to both acute and chronic infections including tuberculosis.[7–10] Shingdang and colleaques reported that the change shows the overall production and breakdown of proteins due to microbial interactions.[8] In chronic infectious TB disease, the albumin shows a decrease while globulin content shows an increase leading to low albumin to globulin (A/G) ratio.[7] This shows that there are significant alterations in proteins fractions in tuberculosis infections.

The present study therefore, is designed to assess the prognostic value of albumin and albumin/globulin ratio as index of treatment recovery in TB patients especially in resource limited setting.

2. Materials and methods

2.1. Study location

This was a cross-sectional study designed to assess the prognostic value of albumin and albumin globulin ratio in the treatment of pulmonary tuberculosis subjects attending Direct Observed Therapy Short course (DOTS) clinic of the General Hospital, Oron, Oron Local Government Area of Akwa Ibom State, South–South Nigeria. A total of 90 subjects aged between 21 and 52 years were conveniently recruited for this study. 60 (29 males and 31 females) were clinically confirmed PTB subject with no HIV nor malaria co-infections. They were diagnosed based on sputum smear microscopy and radiography, (class 3 TB) according to WHO guidelines.[11] They were further sub-divided into TB subjects on ATT 30(14 females and 16 males) and drug naïve TB (yet to commence ATT) subjects 30(17 females and 13 males). The TB subjects on ATT had been on the DOTS (regimen of Rifampicin (R), Isoniazid (H), Pyrazinamide (Z), and Ethambutol (E) or Streptomycin (S) for eight (8) weeks. The remaining were 30 (15 females and 15 males) aged matched apparently healthy controls from Iquita and Uya metropolis who were not attending the General Hospital, Oron DOTS Clinic.

2.2. Sampling technique

Anthropometric measurements included weight, which was measured with light clothes and without shoes and approximated to the nearest 0.1kg on a mobile lever scale, while height was measured to the nearest 0.1cm using a stadiometer. BMI was calculated as weight (in kilogrammes) divided by the square of height (in meters). The waist circumference was measured by using a flexible, non-stretch measuring tape to measure the waist circumference midway between the lower rib margin and iliac crest with the tape all-round the body in a horizontal position. The hip circumference was taken as the measurement around the widest portion of the buttocks, with the tape parallel to the floor. Measurements were recorded to the nearest centimetre. The WHR was calculated as waist circumference divided by hip circumference.

5ml of whole blood was collected from each subject using aseptic venipuncture from the cubital fossa into labelled plain test tubes. The samples were allowed to clot, and then centrifuged at 3500 rpm for 5 minutes. The sera was then transferred into properly labelled plain tubes in aliquots and stored at −20 °C until assayed for total protein and albumin.

2.3. Ethical approval and informed consent

Ethical approval for this study was obtained from the ethics committee of the Ministry of Health Headquarters, Uyo, Akwa Ibom State while the informed consent was obtained from all the participants before enrolment into the study.

2.4. Inclusion/exclusion criteria

Subjects who were clinically confirmed to be infected with pulmonary TB, with no co-existing HIV or malaria infections and who were yet to commence ATT were recruited. Subjects who had been on ATT for eight (8) weeks were also included. Subjects with extra-pulmonary TB were excluded. Subjects who were co-infected with HIV, malaria parasite infection and were younger than 21 or older than 52 years of age were all excluded from the study.

2.5. Methodology

Serum total protein was determined using Biuret method as described by Dale.[12]

Principle: The Biuret test (Piotrowski's test) is a chemical test used to detect the presence of peptide bonds. In the presence of peptides, a copper (II) ion forms violet coloured coordination complexes in an alkaline solution.

Serum Albumin was determined using BromoCresol Green (BCG) method as described by Savoury *et al*[13]

Principle: The measurement of serum albumin is based on its quantitative binding to the indicator BCG. Albumin at pH 4.2 is sufficiently cationic to bind the anionic dye bromocresol green (BCG) to form a blue-green coloured complex. The intensity of the blue green colour is directly proportional to the albumin concentration in the specimen when the absorbance is read at 620–630nm.

Serum globulin concentration was obtained by subtracting values of serum albumin from that of total serum protein. The value for albumin-globulin ratio was obtained by dividing albumin value by globulin value.

2.6. Statistical analysis

The Statistical Package for Social Science, SPSS version 20.0 software (SPSS Inc., Chicago, IL USA) for windows was used, groups mean ± SD was calculated for each parameter and significant difference between means evaluated using analysis of variance (ANOVA). T-test was used to assess variation between groups, while $p \leq 0.05$ was considered as statistically significant.

3. Results

3.1. Anthropometric parametres in TB subjects on ATT, drug naive TB subjects and control subjects

The results showed that BMI (kg/m^2) in drug naive TB subjects (19.25 ± 2.65) and in the TB subjects on ATT (20.30 ± 2.80) was significantly lower when compared to control subjects (24.58 ± 3.05) (p = 0.000). Similarly, waist and hip circumferences (cm) of the drug naive TB subjects (50.12 ± 1.34, 70.58 ± 2.00) and the TB subjects on ATT (51.04 ± 2.88, 70.46 ± 2.65) were significantly lower when compared to control subjects (52.24 ± 4.46, 72.23 ± 3.44) (p = 0.038, 0.025). However, the mean value of WHR in drug naive TB subjects (0.71 ± 0.03) and in TB subjects on ATT (0.73 ± 0.04) were not statistically significant when compared to control subjects (0.72 ± 0.05) (p = 0.274). Also, the mean weight (kg) of TB subjects on ATT (58.17 ± 4.62) when compared with that of the drug naive TB subjects (51.47 ± 10.50) was not statistically significant (p = 0.111) (See Table 1).

3.2. Levels of Total protein, Albumin, Globulin and Albumin-Globulin ratio in TB subjects on ATT, drug naive TB subjects and control subjects

The results showed that the mean serum total protein levels (g/dl) in TB subjects on ATT (8.82 ± 1.64) and in the drug naive TB subjects (9.02 ± 1.77) were significantly higher when compared with the control subjects (7.78 ± 0.89) (p = 0.004).

In TB subjects on ATT, the mean (±SD) serum albumin (g/dl) was significantly higher (5.41 ± 1.47) when compared with control subjects (3.93 ± 1.05) (p = 0.000). In contrast, the drug naive TB subjects had a significantly lower mean serum albumin (2.78 ± 0.77) when compared with the control (3.93 ± 1.05) (p = 0.000).

Mean serum globulin (g/dl) level in TB subjects on ATT (3.41 ± 1.52) was significantly lower when compared to their counterparts not on ATT (6.23 ± 1.86) (p = 0.000). However, both groups of TB subjects had significantly higher mean serum globulin levels when compared with control subjects (3.85 ± 1.40) (p = 0.000). Similarly, the mean level of albumin-globulin ratio was significantly higher in TB subjects on ATT (2.33 ± 1.97) but decreased significantly in drug naive TB subjects (0.52 ± 0.31) when compared with control subjects (1.09 ± 0.56) (p = 0.000 respectively). (See Table 2).

Table 1 – Anthropometric parameters in TB subjects on ATT, drug naive TB subjects and control subjects.

Groups	Height (m)	Weight (kg)	BMI (kg/m2)	WHR
TB subjects on ATT (A) n = 30	1.69 ± 0.15	58.17 ± 4.62	20.30 ± 2.80	0.73 ± 0.04
Drug naive TB subjects (B) n = 30	1.64 ± 0.14	51.47 ± 10.50	19.25 ± 2.65	0.71 ± 0.03
Control (C) n = 30	1.72 ± 0.14	73.33 ± 12.86	24.58 ± 3.05	0.72 ± 0.05
F- value	2.641	23.079	29.666	1.314
P- value	0.077	0.000	0.000	0.274
A vs B	0.346	0.111	0.333	0.406
A vs C	0.654	0.000	0.000	0.976
B vs C	0.064	0.000	0.000	0.297

P < 0.05 = Significant. Data was expressed as mean ± SD.

Table 2 – Levels of Total protein, Albumin, Globulin and Albumin-Globulin ratio in TB subjects on ATT, drug naive TB subjects and control subjects.

Groups	TP (g/dl)	Albumin (g/dl)	Globulin (g/dl)	AGR
TB subjects on ATT (A) n = 30	8.82 ± 1.64	5.41 ± 1.47	3.41 ± 1.52	2.33 ± 1.97
Drug naive TB subjects (B) n = 30	9.02 ± 1.77	2.78 ± 0.77	6.23 ± 1.86	0.52 ± 0.31
Control (C) n = 30	7.78 ± 0.89	3.93 ± 1.05	3.85 ± 1.40	1.09 ± 0.56
F- value	6.025	40.486	24.670	14.428
P- value	0.004	0.000	0.000	0.000
A vs B	0.869	0.000	0.000	0.000
A vs C	0.021	0.000	0.476	0.002
B vs C	0.005	0.001	0.000	0.163

P < 0.05 = Significant. Data was expressed as mean ± SD.

4. Discussion

In the present study, BMI and WHR were significantly lower in both TB subjects on ATT and in their drug naive counterparts when compared with the control. This may be attributed to the severe wasting and malnutrition most commonly associated with tuberculosis. The wasting in TB reduces both muscle and fat mass and a considerable length of time may be needed to build up the body protein reserves to the pre-disease state.

The results from the present study also showed that there was no significant difference between the weights of the TB subjects on ATT and their drug naive counterparts. This finding is in line with earlier reports by PrayGod *et al*[14] and Umo *et al*[15] Previous study has attributed it to differences in the contribution of weight gain in different body compartments despite strong anabolic response.[16] Significant decrease in body weight has been a common finding in patients with active tuberculosis, and this has been attributed to the likely combination of associated tissue inflammations and immune responses. The authors noted that weight gain during anti-tuberculosis therapy is unreliable indicator of overall treatment response.[14,15] Bekker *et al*[17] had also earlier reported that clinical and functional recovery often lags behind microbiological cure. Even though weight gain is frequently used as a measure of treatment response in tuberculosis,[18] the results of this study also showed significantly lower albumin and albumin globulin ratio in drug naive TB subjects when compared with control subjects. Depleted serum albumin in drug naive TB subjects is suggestive of a chronic infectious process and may be attributed to oedema or malnutrition. The decrease may also be attributed to several factors such as acute and chronic inflammatory responses, nephrotic syndrome, malnutrition and decreased immunity. This is in consistent with other findings.[7,8] Poor nutritional status in patients with active pulmonary tuberculosis compared with healthy controls has also been reported elsewhere.[19] Other studies have reported reduced plasma albumin and total protein concentration in chronic TB infection.[9,10]

The findings from this present study also showed significantly increased albumin and albumin-globulin ratio among the TB subjects on ATT when compared to their drug naive counterparts. This may be due to some level of improvement occasioned by the ATT regimen. This is in concordance with the findings of Egah *et al*[20] The author noted that increased albumin-globulin ratio is possibly due to the role of albumin as an antioxidant to prevent cellular damage and tissue wasting in TB individuals. The increases observed in serum albumin of the TB subjects on ATT may also be attributed to increased albumin synthesis by the liver which may be directly or indirectly linked to the effect of the anti-tuberculosis therapy (ATT).

The increase in serum total proteins and albumin observed in pulmonary tuberculosis subjects in this study may be attributed to the anti-tuberculosis drugs Isoniazid and Rifampicin suggesting significant improvement with the treatment regimen. This was in line with previous report,[20] and contrary to report by Damburam *et al*[21]The author reported decreased serum levels of total protein and albumin in tuberculosis. This discordance may be due to sample size and differences in patient distribution in different geographical locations. The variations in the level and pattern of serum proteins in TB subjects have been reported to be due to parasitic infestations, culture and socio-economic status.[22]

Increased serum globulin levels in tuberculosis patients were also noted when compared with the apparently healthy controls. This could be attributed to the fact that in infectious diseases such as tuberculosis, serum globulin formation increases significantly as a result of increased immune response where antibodies are produced. Elevated serum globulin in the drug naive TB subjects may be attributed to the host immune response to the TB infection. This was consistent with the findings by Edozien.[23]

The elevated albumin-globulin ratio observed in the present study is a direct consequence of depleted serum albumin (hypoalbuminaemia) and elevated globulin. This is in agreement with some previous findings.[19,21,24] Damburam *et al*[21] attributed the increased serum globulin levels to the host immunologic response to the tubercle bacilli which elicits the production of gamma globulins. Arinola and Igbi[25] also reported high levels of serum IgG and IgM in pulmonary tuberculosis. This observation was in discordance with other reports.[20]

In conclusion, BMI was found to be significantly lower in both drug naive PTB subjects and in PTB subjects on ATT when compared with the control subjects. This may be attributed to the severe wasting and malnutrition commonly associated with tuberculosis infection, and the lag of physical "wellness" behind clinical "wellness". The depletion of serum albumin and significant reduction in the albumin-globulin ratio observed in the drug naive TB subjects is suggestive of chronic infectious process and may be attributed to oedema or malnutrition and may be due to delayed diagnosis.

Authorship statement

Conceptualization: NRU and ISI; Methodology: NRU, CKN, EFA. Software, CKN and SNU; Validation: NRU and ISI; Formal Analysis: CKN, SNU and ICG; Investigation: CKN, NRU, EFA and ICG; Resources: CKN and SNU; Data curation: CKN, SNU, EFA and ICG; Writing – Original Draft Preparation: NRU, CKN; Writing – Review & Editing: NRU, CKN, ISI, SNU EFA, ICG; Visualization: CKN, and SNU; Supervision: NRU and ISI; Project Administration: CKN.

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Appendix A. Supplementary data

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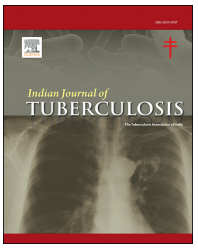

Original Article

Prevalence of p-glycoprotein (PGP) expression, function and its effect on efficacy of rifampicin in patients with lymph node tuberculosis

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ABSTRACT

Objective: P-glycoprotein (PGP) overexpression may be one of the operating mechanisms of suboptimal responses to antitubercular treatment (ATT) in patients with lymph node tuberculosis. This might become responsible for the development of drug resistance later due to exposure of subtherapeutic concentrations to the mycobacteria. In this study we aim to study the prevalence of PGP expression and function and its relationship with serum concentrations of Rifampicin in consecutive patients with lymph node tuberculosis.
Methods: All newly diagnosed treatment naïve subjects with a confirmed diagnosis of tubercular lymphadenopathy were included in the study and the expression and function of PGP in blood was determined by flowcytometry at baseline and after two months of treatment. Serum levels of Rifampicin was measured at 2 months by high performance liquid chromatography (HPLC). The mean net PGP expression expressed as percent and relative fluorescence indices (RFI) of PGP expression and function respectively was compared at baseline at 2 months and was also correlated with serum rifampicin levels.
Results: The mean net PGP expression, RFI of PGP expression and RFI of PGP function were significantly higher in patients with lymph node tuberculosis as compared to healthy controls and the mean net PGP expression and RFI of PGP expression were significantly higher at 2 months as compared to baseline (25.64 ± 5.18% vs. 27.68 ± 4.89%, 4.34 ± 1.09% vs. 4.95 ± 1.55). There was no significant difference in RFI of PGP expression and RFI of PGP function between the poor-responders and responders at baseline and 2 months however there was a trend towards significantly higher net PGP expression amongst poor responders at baseline. The mean serum rifampicin levels were 10.74 ± 2.36 μg/ml in the responder group and 7.86 ± 1.21 μg/ml in the non-responder group and the difference between the two was statistically significant ($p = 0.004$).

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Conclusions: Overexpression of PGP is common in patients with lymph node tuberculosis and leads to lower concentrations of Rifampicin in blood which subsequently may give rise to development of drug resistance. This is also responsible for poor therapeutic responses in these patients. Nonspecific inhibitors of PGP may be used in conjunction with ATT to augment therapeutic response in such cases.

1. Introduction

India is the highest TB burden country and accounts for nearly one quarter of the global TB burden of nearly 2.8 million new cases per year and nearly 4.1 lakh deaths every year.[1] The MDR-TB (multi-drug Resistant TB) describes strains of tuberculosis that are resistant to at least the two main first-line TB drugs: isoniazid and rifampicin. Extensive Drug-Resistant or XDR-TB (also referred to as Extreme Drug Resistance) is MDR-TB that is also resistant to at least one of the injectable aminoglycosides and a respiratory fluoroquinolone.[2]

Development of mycobacterial drug resistance involves various factors amongst which, genetic alteration on drug target genes are the most common. Another important mechanism is the hindrance of the antibiotic to inhibit the intended target.[3,4] This less discussed mechanism includes decreased permeability or active efflux of the antibiotic from its target cells, which results in its decreased intracellular concentration. This seems to be one of the operating mechanisms in patients with extra-parenchymal disease where microbiological resistance is not present or demonstrable.[3–5] Amongst various mechanisms of resistance to drugs, over expression of p-glycoprotein (PGP), a 170-KDa product of the multidrug resistance 1 (MDR-1) gene, has been reported as the major protein involved in drug resistance.[6–9] PGP overexpression is seen in a host of inflammatory conditions and its role has been extensively studied in autoimmune diseases and malignancies however there is paucity of literature regarding its role in mediating drug resistance in tuberculosis. In general, demonstration of mycobacterium tuberculosis in cultured specimen and drug susceptibility testing gives us the reason for poor response to therapy which is common in parenchymal tuberculosis, however in patients with extra-parenchymal disease there is clinical challenge among non-responders when cultures are not positive and reason for poor response remains elusive. In clinical practice it is commonly seen that patients with extrapulmonary tuberculosis specially lymph node and bone/spinal tuberculosis a relatively longer duration of antitubercular treatment is often required because of suboptimal response even in absence of a demonstrable mono/poly dug resistance. This may be in part due to poor therapeutic concentrations of drug due to over expression of PGP as one of the operating mechanisms and this in turn may also be responsible for development of drug resistance in long run. With this background we planned this study to evaluate this hypothesis among patients with lymph node tuberculosis.

1.1. Objectives

This study aims to study the prevalence PGP among consecutive patients of lymph-node tuberculosis and their relationship to clinical response and anti-tubercular therapy (ATT).

1.2. Study design and methods

This was a prospective study conducted in the outpatient clinic of the Department of Pulmonary Medicine at Sanjay Gandhi Postgraduate Institute of Medical Sciences between July 2014 and January 2017. The study protocol was approved by the Institute Ethics Committee and a written informed consent was obtained from all the study subjects.

All newly diagnosed treatment-naïve subjects aged 18–65 years with a confirmed diagnosis of tubercular lymphadenopathy in the age group were eligible for inclusion in the study. Patients were excluded if they met any of the following: (i) patients already received or receiving anti-tubercular therapy; (ii) pregnancy and lactation; (iii) failure to provide informed consent and (iv) human immunodeficiency virus (HIV) infection. Patients on concurrent medications which are known to alter PGP status were also excluded.

The diagnosis of lymph node tuberculosis was established on the presence of compatible clinical picture and demonstration of necrotizing granuloma in cytopathology or histopathology of the lymph node aspirate. All the patients were evaluated clinically and baseline investigations including complete blood counts, liver function tests, renal function tests, urine examination. Tuberculin skin test was performed in all patients. All patients were initiated on standard four drug regimen with intensive phase containing rifampicin, isoniazid, ethambutol and pyrazinamide for 2 months followed by continuation phase containing rifampicin, isoniazid and ethambutol for 4 months. PGP expression and function were assessed at baseline and after 2 months of therapy. Patients were categorized as poor-responders based on clinical response (persistence of fever and constitutional symptoms, no decreases in lymph node size or overall clinical deterioration unexplainable by other reason) at the end of intensive phase of ATT. Serum levels of rifampicin was measured after two months of initiation of treatment. Blood from age and sex matched healthy controls was evaluated for PGP expression and function analysis.

PGP expression on peripheral blood mononuclear cells (PBMCs) was determined by flowcytometry on whole blood whereas PGP function was assessed on PBMCs separated by density gradient centrifugation using Ficoll-hypaque.

Determination of serum levels of rifampicin was carried out with high performance liquid chromatography (HPLC). Samples were taken in morning approximately 2 hours from the last dose of Rifampicin. Briefly, whole blood staining with RBC lysis method was used. 50 μl whole blood was stained with 20 μl of PE conjugated anti PGP antibody (BD Biosciences) and incubated at room temperature for 30 minutes. Then RBCs were lysed and cells fixed with RBC lysing solution (BD Biosciences) for 10 min and washed twice with the PBS, resuspended in PBS and stored at 4 °C in the dark till flow cytometry was performed. Appropriate isotype antibody was analysed in a different tube. Flowcytometric analysis was performed on FACS calibur flow cytometer (Becton Dickinson, Mount view, CA, USA). Analysis was carried out on the lymphocyte-gated population. Ten thousand events were analysed within this gate. Relative fluorescence index (RFI) and percent positive cells were calculated as the measure of PGP expression. p-glycoprotein function was measured in vitro by flowcytometry of total peripheral blood mononuclear cells using a rhodamine 123 efflux assay. 1×10^6 PBMCs were incubated with 0.4μM Rhodamine 123 (Sigma Aldrich) in warm RPMI 1640 (Sigma Aldrich) for 30 min at 37 °C and then washed with ice cold PBS twice to completely remove rhodamine from the medium. Then, rhodamine treated PBMCs were incubated in presence and in absence of PGP inhibitor, 5μM (verapamil), in RPMI 1640 at 37 °C for 180 min followed by washing with ice cold PBS and suspension in PBS. Rhodamine efflux was measured in presence and in absence of verapamil. Mean fluorescence index (MFI) was calculated for each analysis. The difference in the MFI measured in presence and absence of verapamil was considered as functionality of the PGP.

1.3. *Statistical analysis*

The mean levels of PGP expression and function between the cases and controls was compared by independent t-test, both at baseline and after 2 months. Within the group, PGP expression and function parameters at baseline and after 2 months of therapy were compared by paired t-test. The mean change in PGP expression and function between the two groups was compared by independent t-test. Correlation analysis was performed using Pearson correlation coefficient. There was no background data available regarding PGP expression on PBMCs of patients with tuberculosis. Therefore, no formal sample size calculation could be performed for this pilot study.

2. Results

A total of 42 patients were enrolled in the study of which follow up data was available for 37 patients. Mean age 29.91 ± 13.44 years and male: female ratio was 2:3. Cervical lymphadenopathy was the most common site involved and apparent swelling was the most common presenting symptom followed by loss of appetite and weight (Table 1). PGP expression and function were equally distributed across the all ages and both the genders. All patients received standard 4 drug regimen (HRZE) as per protocol and tolerated the treatment well except two patients who had drug induced liver injury requiring temporary replacement with modified regimen. Both the patient tolerated the drugs on reintroduction. All the patients in the poor-responder group required prolongation of treatment duration ranging from 12 to 18 months however in the responder group treatment duration was 6–9 months.

Table 1 – Clinical characteristics.

Parameter	Results ((n = 37))
Age	29.91 ± 13.44
Males	14
Females	23
Fever	21
Weight Loss	21
Appetite Loss	22
Apparent swelling	34
Location of lymphadenopathy	
Cervical	20
Supraclavicular	3
Mediastinal	3
Generalised	11
Comorbidities	
Type 2 Diabetes Mellitus	2
Hypertension	1
Hypothyroidism	1
Responders	30
Non responders	7

Values are expressed as mean ± SD unless specified.

All patients in our cohort had high PGP expression and function as measured in serum samples as compared to PGP expression in healthy population. The mean net PGP expression, RFI of PGP expression and RFI of PGP function was 25.64 ± 5.18%, 4.34 ± 1.09% and 107.14 ± 45.63% respectively at baseline (Table 2). These values were significantly higher as compared to healthy controls. At 2 months the mean net PGP expression, RFI of PGP expression and RFI of PGP function was 27.68 ± 4.89%, 4.95 ± 1.55% and 89.36 ± 50.76% respectively. The mean net PGP expression and RFI of PGP expression was significantly higher at 2 months as compared to baseline ($p = 0.019, 0.031$) (Table 2).

There was no significant difference in net PGP expression, RFI of PGP expression and RFI of PGP function between the non-responders and responders at baseline and 2 months. Although the values did not reach statistical significance but there was a trend towards higher PGP expression among non-responders at baseline. It was noteworthy that at 2 months the net PGP expression remained unchanged from the base line (Table 3). It was interesting observation that the mean serum rifampicin levels were 10.74 ± 2.36 μg/ml in the responder group and 7.86 ± 1.21 μg/ml in the non-responder group and the difference between the two was statistically significant ($p = 0.004$). Majority of patients did not have co-morbidity except for 2 patients with Type 2 Diabetes Mellitus and one patient with hypertension and hypothyroidism each (Table 1). There was no significant difference in mean PGP expression and function even after excluding these patients.

3. Discussion

Patients with lymph node tuberculosis had significantly increased expression and function of PGP as compared to

Table 2 – PGP expression and functional indices.

	Healthy controls	Base line (n = 37)	At 2 months (n = 37)	p value
Net PGP expression (%)	4.19 ± 1.49	25.64 ± 5.18	27.68 ± 4.89	**0.019**
RFI of PGP expression (%)	3.50 ± 1.49	4.34 ± 1.09	4.95 ± 1.55	**0.031**
RFI of PGP function (%)	35.76 ± 25.67	107.14 ± 45.63	89.36 ± 50.76	0.276

Values are expressed as mean ± SD unless specified.

Table 3 – PGP expression and functional indices among responders and non-responders.

	Responder (n = 30)		Non responder (n = 7)		p value	
	Baseline	At 2 months	Baseline	At 2 months	Baseline	2 months
Net PGP expression (%)	24.92 ± 4.59	27.44 ± 4.81	28.77 ± 6.69	28.71 ± 5.35	0.076	0.54
RFI of PGP expression (%)	4.30 ± 1.04	5.04 ± 1.67	4.51 ± 1.34	4.55 ± 0.78	0.655	0.462
RFI of PGP function (%)	40.83 ± 21.04	50.81 ± 22.46	66.20 ± 40.30	50.55 ± 18.58	0.230	0.978
Rifampicin levels (μg/ml)	–	10.74 ± 2.36	–	7.86 ± 1.21	–	**0.004**

Values are expressed as mean ± SD unless specified.

healthy controls and PGP expression significantly increased after 2 months of therapy as compared to baseline. This appears biologically plausible also because it has been demonstrated in recent pharmacokinetic studies that rifampicin may induce p glycoprotein and consequently increase its expression on mononuclear cells.[10] It was also noticeable that there was a trend towards higher PGP expression in patients who had poor clinical response to antitubercular treatment at the end 2 months (poor-responder group).

PGP functions as an energy-dependent trans-membrane efflux pump. It is usually expressed in a wide variety of healthy tissues and cells, including the epithelial cells of the intestine, hepatocytes, the adrenal glands, renal proximal tubules and the endothelium of blood–brain and maternal–fetal barriers, as well as lymphocytes.[11,12] The physiological role of PGP has been defined as the detoxification and transport of metabolites and secretion of various pro-inflammatory cytokines.[11]

Rifampicin is one of the main agents in the chemotherapy of M. tuberculosis infections. The bioavailability of rifampicin is an important factor for optimal results treatment of TB; reduced bioavailability can result in the development of drug resistance and subsequent treatment failure.[13,14] The normal therapeutic concentration of rifampicin following an oral dose, as reported in literature are attained within 2 hours with a maximum concentration (Cmax) ranging between 4 and 32 μg/ml.[15–17] In a recent study it has been hypothesized that patients showing poor bioavailability of anti-tubercular drugs may have over-expression or increased function of cytochrome P450 3A4 (CYP3A4) and/or p-glycoprotein (PGP), since rifampicin is substrate as well as an inducer of both PGP and CYP3A4.[18] Also in an experimental study it has been demonstrated that increased expression of PGP can cause induction of CYP3A4 and resultant decreased serum concentration of rifampicin. It was observed that in mouse models having overexpression of PGP the therapeutic drug concentration was not achieved.[19] Thus, it is likely that transport of rifampicin by PGP is an important element in drug activity, and that variation in human expression of PGP contributes to individual variability in rifampicin disposition. With this background it can be inferred that in population with high expression of PGP can have poor bioavailability of anti-tubercular drugs which can result in poor response and subsequently may also lead to development of drug resistance at genetic level due to sub therapeutic drug concentrations for a longer period. The same was found in our cohort also and it was observed that serum levels of rifampicin were significantly lower at the end of 2 months in patients who had higher expression of PGP i.e the non-responder group and the difference in serum levels of rifampicin was statistically significant between the responder and non-responder group (P = 0.004). Although the serum levels were within therapeutic range but were towards the lower limit of normal range. This may have an impact on overall therapeutic concentrations at the tissue level which could be responsible for poor response amongst the patients in our cohort. It is noteworthy that although the values did not reach statistical significance but was a trend towards higher PGP expression among the poor-responder group. PGP To increase bioavailability these patients may be candidates for co-administration of inhibitors of PGP which may result in better drug penetration and absorption and subsequent better response to therapy and prevention of development of drug resistance. One of the inhibitors which has been evaluated with rifampicin in pharmacokinetic studies is piperine which is an alkaloid found naturally in plants belonging to the *Piperaceae* family, such as *Piper nigrum* L, commonly known as black pepper and *Piper longum* L, known as long pepper. Piperine is known to inhibit PGP and CYP 3A4 and thus acts as a bioenhancer that increases the bioavailability and bioefficacy of a particular drug. In a recent study it was showed that after oral administration there was significant enhancement in the Cmax and area under the curve (AUC) and thus bioavailability.[20] Similarly, in a small clinical trial it was demonstrated that a fixed dose combination of 200 mg of rifampicin and 10 mg of piperine the rate of sputum conversion was faster as compared to standard treatment regimen.[21] A similar recent larger trial showed similar results in cohort of 216 sputum positive patients.[22] These results indicate that

piperine can increase the bioavailability of rifampicin and improve clinical results but most of the trials are done with a fixed dose combination of 200mg rifampicin and 10 mg piperine however it appears logical that patients over-expressing PGP may require larger doses of rifampicin which will subsequently result in adequate therapeutic concentrations of rifampicin in blood as well as in tissue. Larger well controlled studies are required to document this fact which may be helpful in patients with extrapulmonary tuberculosis specially lymph node tuberculosis where longer treatment duration is required for satisfactory results.

Small sample size was the main limitations in our study and being a tertiary care centre there is an inherent chance of selection bias. Sample size was small because of the fact that treatment naïve patients were required for the study and majority of patients attending our institute were referred patients who had already been initiated on antitubercular therapy before coming to the institute.

4. Conclusions

There is high expression of PGP in patients with lymph node tuberculosis and it is inversely associated with serum rifampicin levels. This has important implications on response to antitubercular treatment. PGP inhibitors may be used along with standard doses of antitubercular drugs as bioenhancers to increase bioavailability of specific drugs specially rifampicin and isoniazid for optimal results to therapy.

Conflicts of interest

The authors have none to declare.

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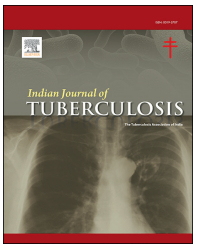

Original article

COVID-19 and tuberculosis: A mathematical model based forecasting in Delhi, India

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ABSTRACT

Background: There is emerging evidence that patients with Latent Tuberculosis Infection(LTBI) and Tuberculosis(TB) disease have an increased risk of the SARS-CoV-2 infection and predisposition towards developing severe COVID-19 pneumonia. In this study we attempted to estimate the number of TB patients infected with SARS-CoV-2 and have severe disease during the COVID-19 epidemic in Delhi, India.

Methods: Susceptible-Exposed-Infectious-Recovered (SEIR) model was used to estimate the number of COVID-19 cases in Delhi. Assuming the prevalence of TB in Delhi to be 0.55%, 53% of SARS-CoV2 infected TB cases to present with severe disease we estimated the number of SARS-CoV2 infected TB cases and the number of severe patients. The modelling used estimated R_0 for two scenarios, without any intervention and with public health interventions.

Results: We observed that the peak of SARS-CoV-2-TB co-infected patients would occur on the 94th day in absence of public health interventions and on 138th day in presence of interventions. There could be 20,880 SARS-CoV-2 infected TB cases on peak day of epidemic when interventions are implemented and 27,968 cases in the absence of intervention. Among them, there could be 14,823 patients with severe disease when no interventions are implemented and 11,066 patients with severe disease in the presence of intervention.

Conclusion: The importance of primary prevention measures needs to be emphasized especially in TB patients. The TB treatment centres and hospitals needs to be prepared for early diagnosis and management of severe COVID-19 in TB patients.

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1. Introduction

The on-going pandemic of COVID-19, a viral pneumonia like illness, emerged in Wuhan, China in December and has since spread across 210 nations.[1] Till date (21.4.2020), there have been 2 397 216 confirmed cases and 162 956 deaths due to the disease.[2] Most cases SARS-CoV-2 infection has minimal symptoms and are self-limiting. However, it is also well-established that patients with underlying comorbidities especially diabetes, hypertension, coronary heart disease, tuberculosis (TB) and the elderly are at significantly increased risk of complications and death due to COVID-19.[3,4]

Tuberculosis is a bacterial disease predominantly affecting the lung. During 2017, an estimated 10 million new TB disease cases occurred globally,[5] while 2.8 million cases were registered in India, the highest in the world.[6] Although, TB-related mortality declined from 56/100000/year in 2000 to 32/100000/year but still caused an estimated 1.7 million deaths in 2016 in India.[6] Furthermore, the prevalence of latent mycobacterium tuberculosis infection (LTBI) is also very high (40%) in India.[7]

Even though the portal of entry is upper respiratory tract for both TB and COVID-19, the association between co-infection of severe influenza and pulmonary TB disease remain inconclusive.[8,9] However, there is emerging evidence that patients with LTBI and TB disease have an increased risk of the SARS-CoV-2 infection and predisposition towards developing severe COVID-19 pneumonia.[4] Any relationship of COVID-19 and TB is particularly relevant for the public health system in India since India is one of the major contributors in burden due to TB with highest number of TB cases in the world.[5] Also, isolation of cases and contacts for controlling COVID-19 can be problematic in low socioeconomic TB households.[10]

Under these circumstances and considering the large burden of active tuberculosis patients in India along with localized, hotspot and community transmission of COVID-19, estimation of the infection and morbidity due to COVID-19 epidemic among TB patients in India is warranted. This would also enable allocation of resources towards the development and implementation of effective public health interventions in such vulnerable populations. With this background in this study we attempted to estimate the number of TB patients infected with SARS-CoV-2 and have severe disease during the COVID-19 epidemic in Delhi, India.

2. Materials and methods

The estimations in this study are based on Susceptible-Exposed-Infectious-Recovered (SEIR) model.[11] This is a compartmental model which is used to predict the infectious disease epidemic. The model is summarized with the following chart and equations.[12]

$$dS/dt = -\beta IS/N$$

$$dE/dt = \beta IS/N - E/l$$

$$dI/dt = E/l - \gamma I$$

$$dR/dt = \gamma I$$

where N is the total population S is the number of susceptible population in the community, E is the number of exposed people, I is the number of infected people, R is the number of recovered people, β is the transmission coefficient, γ is the recovery coefficient. The R_0 for COVID-19 was calculated for Delhi by multiplying the population density ratio of Delhi and Wuhan with R_0 for Wuhan.[12] The Markov's probability model was used to estimate the number of mild/moderate and severe disease.[13]

Two scenarios were considered to estimate the number of infected COVID-19 cases, (i). Without any public health intervention, (i) With public health interventions like lock down, social distancing and isolation of cases and contacts. The proportion contributed to case pool was 48.5% for household contact, 30.5% for workplace contact, 20.8% for community contact.[14] The assumed reduction achieved by the intervention lockdown, social distancing, case and contact isolation was 25% for household contacts, 96% for workplace contacts, and 70% for community contacts. Case isolation was done from day zero in Delhi, lock down was implemented from 20th day of reporting of reporting of the index case till 3rd May 2020 (62nd day). We also assumed that the effect of lockdown and social distancing interventions may be shown after 7 days which is half of maximum incubation period. The effective reproductive rate (R_t) under public health interventions was calculated by multiplying the reduction fractions assumed for the intervention with R_0. The parameters used for modelling are provided in Table 1. The number of notified cases of tuberculosis in 2018 for Delhi was obtained from India Tuberculosis report 2019 and was considered as the estimated prevalence of tuberculosis case in Delhi. The proportion of SARS-CoV-2 infected TB cases with severe disease was considered as 53% as per the results of a study in China.[10]

Ethics: There are no ethical concerns related to the study since all the data are taken from the official public domains of respective institutions.

3. Results

Our study estimated the number of SARS-CoV-2 infected active TB cases during COVID-19 epidemic in Delhi. It was observed that the implementation of public health interventions would delay the peak and leads to flattening of the epidemic curve. We found that the peak of SARS-CoV-2-TB co-infected patients would occur on the 94th day in absence

Table 1 – Parameters used in SEIR model for COVID-19 outbreak in Delhi.

Parameters	Value
Delhi population[a]	1.9 crore[19,20]
Date of reporting of index case	02.03.2020
Incubation period	5 days[8,21,22]
Time to recovery	7 days (mild disease) and 15 days (severe disease)[22]
Average infectious period	10 days[23]
Proportion of asymptomatic cases	30%[24]
Proportion of mild/moderate disease among symptomatic cases	80%[22]
Proportion of severe disease among symptomatic cases	20%[22]
Case fatality rate	3.8%[25]
Basic reproductive rate (R_0) for Wuhan	3.28[26]
Population density of Delhi	11,320[27]
Population density of Wuhan	6000[12]
Estimated R_0 for Delhi[b]	6.18
Notification of tuberculosis cases in Delhi	505 per 100,000 population[6]
Proportion of COVID-19 infected TB patients who had severe disease	53%[4]

[a] Birth rate and death rate from SRS 2017 was applied to Census 2011 values to calculate the Delhi population.[19,20].
[b] R_0 in Delhi population = (Population density of Delhi/population density of Wuhan)*R_0 in Wuhan population.

of public health interventions. In presence of effective interventions like lockdown for a period 42 days, social distancing, contact tracing and case isolation, the peak would be delayed by 44 days and occur on the 138th day. The estimated number of SARS-CoV-2 infected TB patients during the epidemic in Delhi is depicted in Fig. 1. It is estimated that there could be 20,880 SARS-CoV-2 infected TB cases on peak day of epidemic when interventions are implemented and 27,968 SARS-CoV-2 infected TB cases if no interventions were implemented.

We also observed that on peak day there could be 14,823 patients with severe disease when no interventions are implemented and 11,066 patient with severe disease when the above mentioned public health interventions are implemented (Fig. 2). There could be 13,145 SARS-CoV-2 infected TB cases with mild to moderate disease on peak day in the absence of any intervention and 9813 SARS-CoV-2 infected TB cases with mild to moderate disease on peak day on implementing the necessary interventions mentioned above.

4. Discussion

The present study estimated the probable peak count of COVID-19 cases among TB patients using SEIR compartmental model. We also estimated the SARS-CoV-2 infected TB patients with mild-moderate disease and severe disease, both in event of public health interventions and their absence respectively. TB patients in developing countries are likely to be undernourished (low BMI) with a weakened immune system which might predispose to superadded infections even in those patients initiated on DOTS but in the early treatment stages.[15]

The TB patients with COVID-19 are at higher risk of developing severe disease and may become critically ill requiring mechanical ventilation.[4] Even with the implementation of public health interventions, we observed there could be 11,066 SARS-CoV-2 infected TB patients with severe disease. There are evidences that 62% of the critically ill

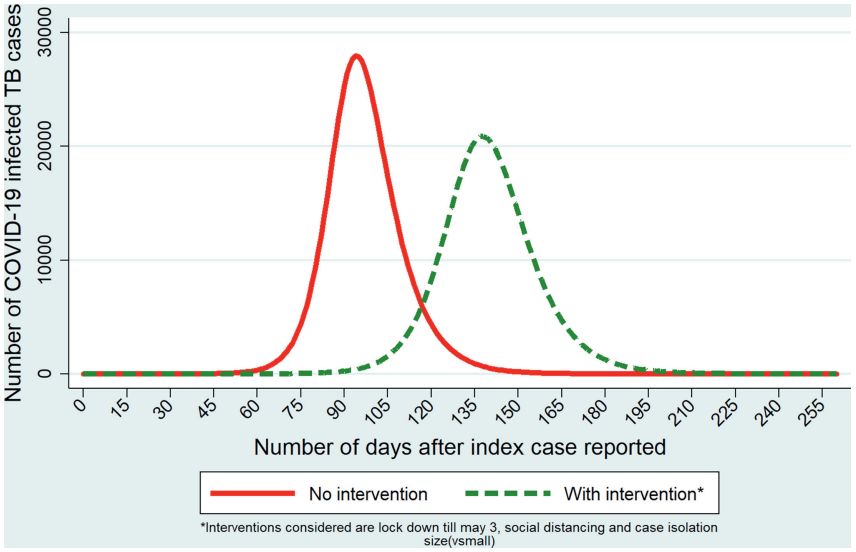

Fig. 1 – Estimated COVID-19 infected Tuberculosis patients during the outbreak in Delhi.

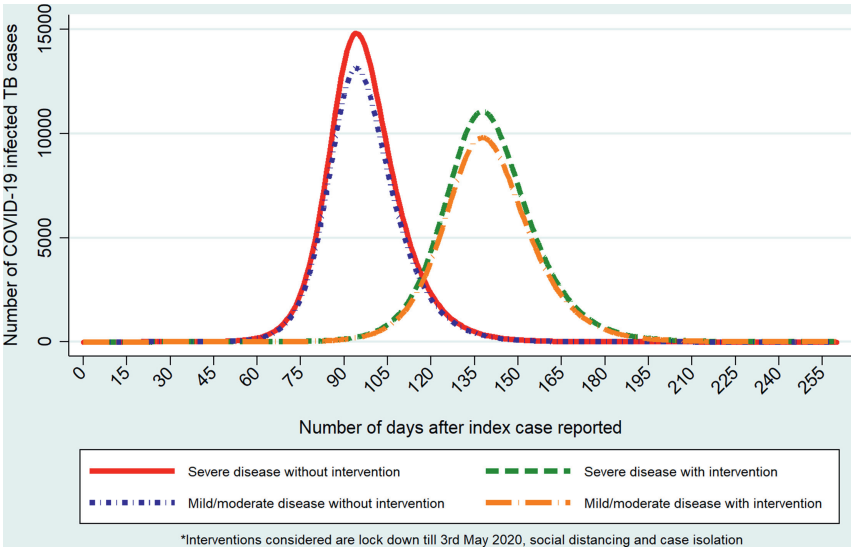

Fig. 2 – Estimated COVID-19 infected Tuberculosis patients with severe disease in Delhi.

patients and 81% of the patients requiring mechanical ventilation had succumbed to death.[16]

Our results have few implications for the National Tuberculosis Elimination Program (NTEP) of India. First, since the rate of severe COVID-19 is higher among TB patients, the program needs to focus of primary prevention measures like adequate ventilation, queuing with physical distancing of atleast 1 meters and preferable airborne control measures needs to be maintained in all TB care centres to reduce the risk of transmission of SARS-CoV2 infection. Second, the TB patients and their family members needs to be educated on measures to protect against COVID-19 including respiratory hygiene, regular hand washing with soap water, social distancing and avoid touching of the face, mouth and eyes. Third, there is an urgent need for surveillance of TB patients on DOTS anti-tubercular therapy reporting for symptoms of flu-like illness that could be suggestive of COVID-19 disease. Particular attention is required for TB cases reporting with acute breathlessness which can be symptomatic of severe COVID-19 disease. Furthermore, ensuring continuing of DOTS by provision of timely refills to patients with TB to fulfil obligations under the universal health care requirements is required. This would also potentially reduce their susceptibility to SARS-CoV2.[17] Resolution of any TB drug related stockouts or associated procurement challenges warrant urgent prioritization.[17]

The strength of our study is that we used SEIR model to estimate the number of infected patients with COVID-19 which will help the policy makers to design effective public health strategies to control the epidemic. SEIR model is a compartmental model and assumes closed population which might be violated in the actual scenario.[18] However, because of lockdown the migration is effectively controlled in Delhi. The results of the study needs to be interpreted with caution since the estimation of excess risk of severe disease of COVID-19 in TB patients was based on a study in China having a small sample size.[4] However, due to lack of other studies from high burden TB countries we used the results of this study.

The prevalence of TB in general population might not be the same as the prevalence of TB in COVID-19 patients. However because of the limited evidences related to the increased risk of COVID-19 among tuberculosis patients, the study used the above assumption.

In conclusion, our study estimated that even with implementation of public health interventions, 20,880 SARS-CoV2 infected TB cases and among them, 11,066 patients might present with severe disease during peak days of the epidemic curve and have high risk of mortality. So, the importance of primary prevention measures needs to be emphasized especially in TB patients. The TB treatment centres and hospitals needs to be prepared for early identification and management of COVID-19 in TB patients.

Conflicts of interest

The authors have none to declare.

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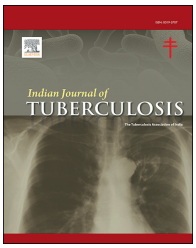

Original article

Tuberculosis and risk of coronary heart disease: A systematic review and meta-analysis

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ABSTRACT

Background: Increased risk of coronary heart disease has been observed in several chronic inflammatory disorders, including chronic infection. However, data on the association between tuberculosis and risk of coronary heart disease are limited.
Methodology: This systematic review and meta-analysis identified all cohort studies that compared the risk of coronary heart disease among patients with tuberculosis versus individuals without tuberculosis and summarized their results together. Literature search was independently conducted by two investigators using MEDLINE and EMBASE database up to August 2019. Point estimates and standard errors from each study were pooled together using the generic inverse variance method of DerSimonian and Laird.
Results: A total of four cohort studies met the eligibility criteria and were included into the meta-analysis. The pooled analysis found that patients with tuberculosis have an increased risk of developing coronary heart disease with the pooled risk ratio of 1.76 (95% CI, 1.05–2.95; I^2 of 97%).
Conclusion: A significantly increased risk of coronary heart disease among patients with tuberculosis was demonstrated by the current study.

1. Introduction

Tuberculosis continues to be a major public health concern that is responsible for approximately 1.6 million deaths per year worldwide.[1] Approximately 10% of individuals who contact with air-borne *Mycobacterium tuberculosis* will develop active tuberculosis in their lifetime, resulting in around 10 million new diagnosis of active tuberculosis each year.[1,2] The pathogenesis of tuberculosis is characterized by complex interaction between host cell-mediated immune response and survival of the mycobacterium.[3] Latent tuberculosis is the condition in which persistent host immune response forms granuloma that limit proliferation of the mycobacterium. Patients with latent tuberculosis are typically asymptomatic and are usually diagnosed by tuberculin skin test and interferon gamma release assay. Once mycobacterial proliferation is not properly controlled by the host immune, patients become symptomatic and are diagnosed with active tuberculosis.[3]

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Coronary heart disease accounts for about one-third of all deaths in individuals over the age of 35.[4] This condition is a result of narrowing of atherosclerotic coronary artery and thrombotic occlusion of a ruptured or eroded atherosclerotic plaque.[5] Known risk factors of coronary heart disease include smoking, diabetes mellitus, hypertension and dyslipidemia.[6,7] Patients with chronic inflammatory conditions such as rheumatoid arthritis, systemic lupus erythematosus and inflammatory bowel diseases are also recognized to have premature atherosclerosis leading to a higher risk of coronary heart disease.[8–10] Furthermore, inflammation caused by infection of certain pathogens have also been linked to atherosclerosis. These include, but not limited to, *Chlamydia pneumoniae*, *Porphyromonas gingivalis*, *Helicobacter pylori*, Influenza A virus, hepatitis C virus, cytomegalovirus and human immunodeficiency virus.[11]

Similarly, patients with tuberculosis may also have a higher inflammatory burden and are more susceptible to coronary heart disease, although this relationship is still not well-established due to limited evidence.[12–15] The current study aimed to comprehensively investigate the risk of developing coronary heart disease among patients with tuberculosis by identifying all available studies and summarizing their results together.

2. Methods

2.1. Information sources and search strategy

Two investigators (W.W. and N.C.) independently performed systematic literature review using EMBASE and MEDLINE database from inception to August 2019 to identify all published studies that examined the risk of coronary heart disease among patient with tuberculosis infection, compared to individuals without tuberculosis infection. The search strategy that included the terms for "tuberculosis" and "coronary heart disease" is available as supplementary data 1. Moreover, references of the included studies were manually reviewed to identify any additional relevant articles. This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement, which is available as supplementary data 2.

2.2. Selection criteria

Eligible study must be cohort study that consisted of one cohort of patients with tuberculosis and another cohort of individuals without tuberculosis. The study must follow them for incident coronary heart disease. Relative risk (RR), incidence rate ratio (IRR), hazard risk ratio (HR) or standardized incidence ratio (SIR) with associated 95% confidence interval (CI) comparing the incidence of coronary heart disease between the two groups must be reported.

2.3. Data extraction

A standardized data collection form was used to extract following details: last name of the first author, country where the study was conducted, study design, year of publication, number of participants, recruitment of participants, methods used to make the diagnosis of tuberculosis and coronary heart disease, follow-up period, baseline characteristics of participants, confounders adjusted in multivariate analysis and adjusted effect estimates with corresponding 95% CI. The quality of the cohort studies included into this meta-analysis was appraised by Newcastle–Ottawa quality assessment scale comprising of three aspects: (1) recruitment of participants for each cohort, (2) comparability between cases and comparators and (3) ascertainment of the outcome of interest.[16]

2.4. Statistical analysis

All of the statistical analysis was performed utilizing Review Manager 5.3 software from the Cochrane Collaboration (London, United Kingdom). Point estimates and standard errors from each study were pooled together using the generic inverse variance method of DerSimonian and Laird, which assigns the weight of the study in reverse to its variance.[17] Random-effect model, rather than a fixed-effect model, was used as the assumption of fixed-effect model that every study should give rise to the same result is not true under almost all circumstances, especially for meta-analysis of observational studies. Statistical heterogeneity was assessed by Cochran's Q

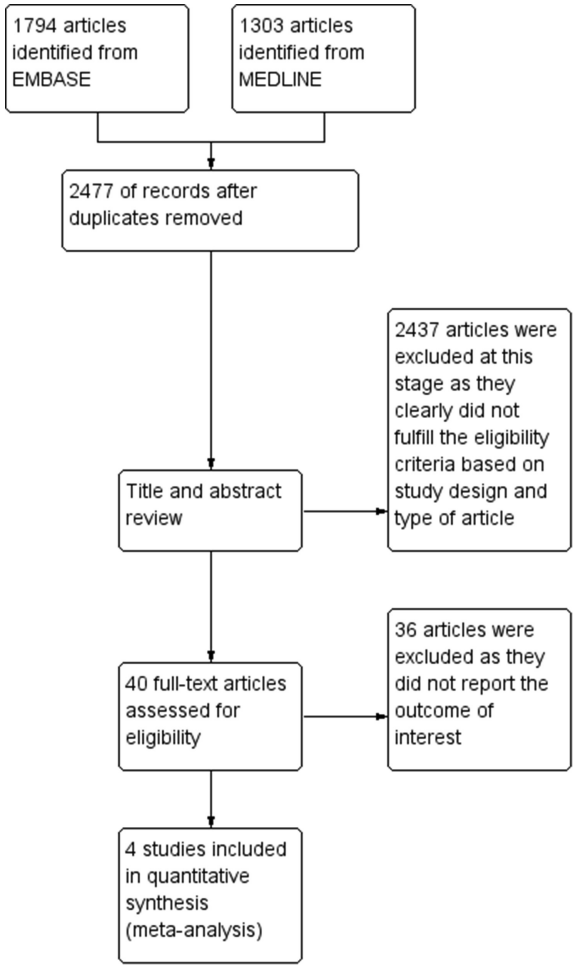

Fig. 1 – Literature review and study selection process.

Table 1 – Main characteristics of the cohort studies included in the meta-analysis.

	Sheu et al. [15]	Chung et al. [12]
Country	Taiwan	Taiwan
Study design	Retrospective cohort	Retrospective cohort
Year of publication	2010	2014
Total number of participants	Patients with TB: 2283 Comparators: 6849	Patients with TB: 10,168 Comparators: 40,672
Recruitment of participants	Patients with TB were identified from the LHID database from January 1st, 2000 to December 31st, 2003. This database is derived from the Taiwan National Health Insurance that covers 98% of residents of Taiwan. Comparators without TB were randomly selected from the same database.	Patients with TB were identified from the NHIRD database from January 1st, 1997 to December 31st, 2010. This database is derived from the Taiwan National Health Insurance that covers 99% of residents of Taiwan. Comparators without TB were randomly selected from the same database. They were age-, sex-, and month-matched to cases.
Diagnosis of TB	Presence of ICD-9-CM for TB, except TB of meninges and central nervous system, in the LHID database for at least three times (ICD-9-CM codes 010, 011, 012, 014, 015, 016, 017, and 018)	Presence of ICD-9-CM code for TB in the NHIRD database for at least three times (ICD-9-CM codes 011–018)
Diagnosis of CHD	Presence of ICD-9-CM codes for CHD in the LHID database	Presence of ICD-9-CM codes for ACS in the NHIRD database for at least three times (ICD-9-CM codes 410–411.1)
Follow-up period	Each patient was tracked for 3 years from the index ambulatory visit	Until new diagnosis of ACS, loss to follow-up, death, withdrawal from insurance system or the end of the study period (December 31st, 2010)
Median duration of follow-up (years)	Patients with TB: 3 Comparators: 3	N/A
Average age of participants (years)	N/A	Patients with TB: 62.9 Comparators: 61.2
Percentage of female	Patients with TB: 36.1% Comparators: 42.9%	Patients with TB: 31.8% Comparators: 31.8%
Comorbidities	Patients with TB: HT: 13.4% DLP: 2.4% DM: 11.6% Malignancy: 11.6% HIV: 0.0% Comparators: HT: 12.9% DLP: 2.1% DM: 6.0% Malignancy: 3.8% HIV: 0.1%	Patients with TB: HT: 38.7% DLP 16.9% COPD 53.7% DM 21.4% CVA 16.6% Comparators: HT: 37.5% DLP 17.5% COPD 28.5% DM 14.9% CVA 13.7%
Variables adjusted in multivariate analysis	Age, sex, HT, DM, DLP, malignancy, monthly income, geographical region and urbanization level	Age, sex and comorbidities
Newcastle–Ottawa score	Selection: 3 Comparability: 2 Outcome: 3	Selection: 4 Comparability: 2 Outcome: 3
	Oh et al. [14]	Huaman et al. [13]
Country	South Korea	USA
Study design	Retrospective cohort	Retrospective cohort
Year of publication	2017	2017

Total number of participants	Patients with TB: 69,023 Comparators: N/A	Patients with TB: 2026 Comparators: 2026
Recruitment of participants	Patients with TB were identified from a national database of South Korea from January 1st, 2010 to December 31st, 2014. Age and sex-stratified population was used as comparators to calculate standardized incidence ratio.	Patients with TB were identified from the database of commercial insurance in the US that covers 15 million patients from January 1st, 2008 to December 31st, 2010. Comparators without TB were randomly selected from the same database. They were propensity scores for 1:1 matched to cases. Propensity score was created from age, sex, metabolic comorbidity, smoking, renal disease and major autoimmune diseases.
Diagnosis of TB	N/A	Presence of ICD-9 code for TB in the database (ICD-9 codes 010.0–018.9)
Diagnosis of CHD	N/A	Presence of ICD-9 codes for AMI in the database (ICD-9 codes 410.0–410.9)
Follow-up period	N/A	Until occurrence of AMI, death, insurance disenrollment or completion of 1-year period
Median duration of follow-up (years)	N/A	N/A
Average age of participants (years)	N/A	N/A
Percentage of female	N/A	Patients with TB: 56.3% Comparators: 56.5%
Comorbidities	N/A	Patients with TB: DM: 50.3% HT: 65.3% DLP: 56.3% Obesity: 16.2% Tobacco use: 17.3% CKD: 16.9% Major autoimmune disease: 19.8% Comparators: DM: 50.5% HT: 64.7% DLP: 55.9% Obesity: 15.2% Tobacco use: 17.8% CKD: 16.7% Major autoimmune disease: 19.6%
Variables adjusted in multivariate analysis	Age and sex	None
Newcastle–Ottawa score	Selection: 2 Comparability: 1 Outcome: 2	Selection: 4 Comparability: 2 Outcome: 3

Abbreviation: ACS: acute coronary syndrome; AMI: acute myocardial infarction; CHD: Coronary Heart Disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CVA: cardiovascular accident; DLP: dyslipidemia; DM: diabetes mellitus; HT: hypertension; ICD: International Classification of Disease; ICD-CM: ICD: International Classification of Disease-Clinical Modification; LHID: Longitudinal Health Insurance Database; N/A: Not available; NHIRD: National Health Insurance Research Database; TB: Tuberculosis; US, United States.

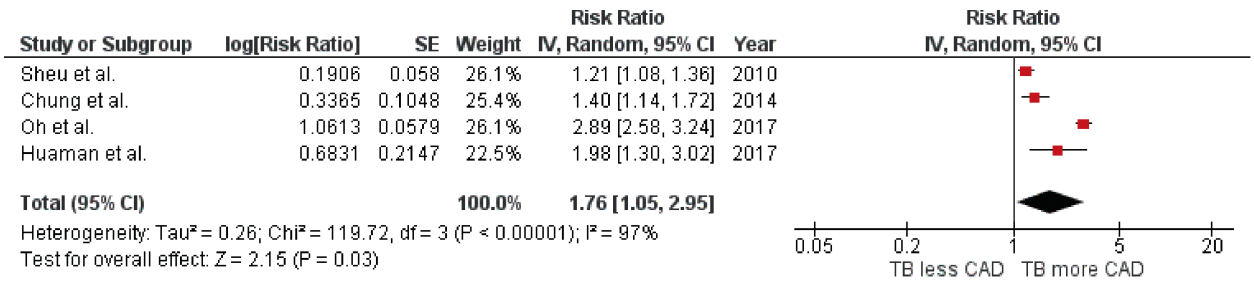

Fig. 2 – Forest plot of this meta-analysis.

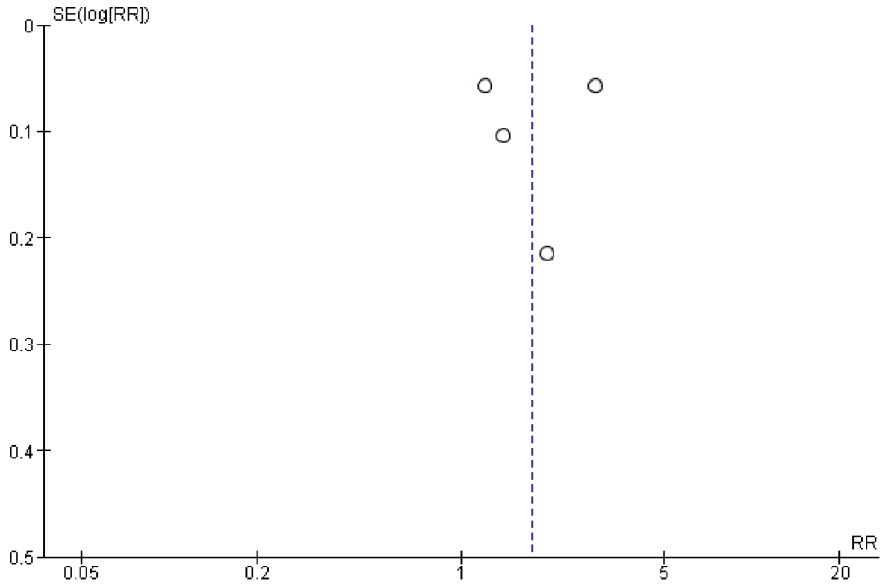

Fig. 3 – Funnel plot of this meta-analysis.

test which is complimented by I^2 statistic. This I^2 statistic quantifies the proportion of total variation across studies that is due to heterogeneity rather than chance. A value of I^2 of 0%–25% represents insignificant heterogeneity, 26%–50% represents low heterogeneity, 51%–75% represents moderate heterogeneity and 76% or higher represents high heterogeneity.[18] Presence of publication bias was assessed by visualization for symmetry of funnel plot.

3. Results

A total of 3097 articles were retrieved from MEDLINE and EMBASE databases in which 620 articles were duplication and were removed, leaving 2477 articles for title and abstract review. A total of 2437 articles were excluded at this stage as they clearly did not fulfill the eligibility criteria based on study design and type of article. Thus, 40 articles underwent full-length article review, in which 36 articles were excluded as they did not report the outcome of interest. Finally, four cohort studies with 83,500 cases of tuberculosis fulfilled the eligibility and were included into the meta-analysis.[12–15] The literature review and study selection process are displayed in Fig. 1. The characteristics and Newcastle–Ottawa assessment scales of the included studies are summarized in Table 1.

3.1. *Risk of coronary heart disease among patients with tuberculosis*

Patients with tuberculosis had a higher risk of developing coronary heart disease than individuals without tuberculosis with pooled risk ratio of 1.76 (95% CI, 1.05–2.95). The statistical heterogeneity was high with an I^2 of 97%. Fig. 2 illustrates the forest plot of this meta-analysis.

3.2. *Evaluation for publication bias*

Funnel plot was applied to assess for the presence of publication bias (Fig. 3). The plot was reasonably symmetric and, therefore, was not suggestive of the presence of publication bias in favor of studies that shows positive association.

4. Discussion

The current study is the first systematic review and meta-analysis to comprehensively identify all cohort studies that

compared the risk of coronary heart disease among patients with tuberculosis to individuals without tuberculosis. The pooled analysis demonstrated approximately 1.8-fold increased risk of coronary heart disease among those with tuberculosis. The exact mechanisms behind this higher risk are not known with certainty but there are few possible mechanisms.[19]

The first possible explanation is that chronic inflammation generated by tuberculosis infection, which is a chronic infection, might accelerate atherosclerosis and, thus, contribute to the increased risk of coronary heart disease.[20] In fact, this phenomenon has seen observed in other chronic inflammatory diseases.[8–10] Inflammation plays a crucial role in development of atherosclerosis.[21] Oxidized by reactive oxygen species, modified low-density lipoproteins (LDL) are scavenged by macrophages, turning them into foam cells. These foam cells, along with extracellular lipid droplets, will form the core of atheroma.[21,22] The infiltration of foam cells and lipid droplets will also induce inflammation in arterial wall causing endothelial dysfunction and activating several leukocyte responses.[21] Enzymes released by activated leukocytes, such as matrix metalloproteinase and cysteine proteases, directly degrade plaque matrix, and cause thinning and disruption of fibrous cap, resulting in thrombosis and coronary artery occlusion.[21] Several proinflammatory mediators, such as TNF-α, IFNγ, IL-1β, IL-6 and IL-17, are generated as immunologic response to tuberculosis infection.[23] These cytokines can alter endothelial functions by increasing endothelial permeability and expression of adhesion molecules, such as ICAM and VCAM, resulting in leukocyte activation, recruitment and adhesion to vascular wall.[24]

The second possible explanation is that tuberculosis infection has been shown to induce autoimmunity through cross-reaction between mycobacterial antigen and human heat shock protein 65 (HSP-65).[25] Responding to stressors, including infection, HSP-65 is translocated from mitochondria to endothelial cell surface and subsequently bound to its serum autoantibody.[26] The binding between HSP-65 and its antibody induced by tuberculosis infection can trigger inflammatory cascades and promotes atherosclerosis.[27] It has been reported that serum HSP-65 antibody level is correlated to the degree of coronary artery calcification, which predicts the risk of developing coronary heart disease.[28]

It is also possible that the observed relationship was not causal. Infection with tuberculosis could just be an indicator of poorer general state of health and/or lower socioeconomic status and the heightened risk of coronary heart disease was actually caused by those factors.[29] This is of particular concern given that two out of four studies did not comprehensively adjust their results for potential confounders.

The current study has some limitations that should be acknowledged. First, between-study heterogeneity was high, suggesting that the results of the included studies may be too different to combine. We believe that the difference in background populations and confounder adjustment were the key sources of the variation. Second, even though the funnel plot was relatively symmetric, it is difficult to exclude the possibility of publication bias with certainty when only a small number of studies were included. Third, all of the included studies were administrative database-based studies that relied on diagnostic codes to identify tuberculosis and coronary heart disease. Therefore, the accuracy and completeness of case identification could be limited.

5. Conclusion

A significantly increased risk of coronary heart disease among patients with tuberculosis was demonstrated by the current systematic review and meta-analysis.

Conflicts of interest

The authors declared no conflict of interest about this article.

Authors' contributions

All authors had access to the data. W.W. and N.C. drafted the manuscript. P.U. edited manuscript. All authors approved the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijtb.2020.01.008.

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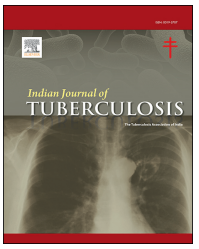

Original article

Tapping private health sector for public health program? Findings of a novel intervention to tackle TB in Mumbai, India

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ABSTRACT

Background: India carries one-fourth of the global tuberculosis (TB) burden. Hence the country has drafted the ambitious National Strategic Plan to eliminate tuberculosis by 2025. To realise this goal, India's Revised National Tuberculosis Control Programme (RNTCP) and partners piloted a novel strategy to engage private-providers for tuberculosis care via a "Private-provider Interface Agency" (PPIA) in Mumbai and other locations.

Intervention: The program mapped and engaged private-providers, chemists, and laboratories; facilitated TB notification via call centers and field staff; provided free tuberculosis diagnostic tests and anti-TB drugs using novel electronic vouchers; monitored quality of care; and supported patients to ensure anti-TB treatment adherence and completion. This report summarises the descriptive analysis of PPIA implementation data piloted in Mumbai from 2014 to 2017.

Findings: The program mapped 8789 private doctors, 3438 chemists, and 985 laboratories. Of these, 3836 (44%) doctors, 285 (29%) laboratories, and 353 (10%) chemists were prioritized and engaged in the program. Over three and a half years, the program recorded 60,366 privately-notified tuberculosis patients, of which, 24,146 (40%) were microbiologically-

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confirmed, 5203 (9%) were rifampicin-resistant, and 4401 (7%) were paediatric TB patients. Mumbai's annual total TB case notification rate increased from a pre-program baseline of 272 per 100,000/year in 2013 to 416 per 100,000/year in 2017. Overall, 42,300 (78%) patients completed the TB treatment, and 4979 (9%) could not be evaluated.

Interpretation: The PPIA program in Mumbai demonstrated that private-providers can be effectively engaged for TB control in urban India. This program has influenced national policy and has been adapted and funded for a country-wide scale up. The model may also be considered in conditions where private-provider engagement is needed to improve access and quality of care for any area of public health.

1. Introduction

India accounts for 27% of the global tuberculosis (TB) burden. Nearly three million people in India are estimated to suffer, and over 480,000 die due to TB annually.[1] Although India's Revised National Tuberculosis Control Programme (RNTCP) has made significant headway and saved millions of lives, TB remains an enormous public health issue in India.[2] India's mixed healthcare market, with a dominant private health-sector (both qualified and non-qualified practitioners) further complicated TB control efforts.[3–6] Reportedly, most TB patients in India prefer private-provider for seeking care.[3,7,8] At least one million estimated TB cases a year are 'missing' or not reported as 'accountably treated'. Most of them are believed to be treated by private-providers, as supported by the massive volume of anti-TB drugs sold in the private-sector.[2,9] However, in the private-sector, cases are often un-reported, treatments are 35%–40% costlier, and providers fail to deliver TB care that adheres to national standards.[7,8,10–13] While seeking care, TB patients consult three providers on average, and incur an average delay of 55–65 days for diagnosis and treatment.[7,14,15] Such delays can contribute to transmission.

Until recently, RNTCP engaged private health-sector through a variety of referral-based approaches included in the RNTCP guidelines. Commonly, in referral-based approaches, private-providers are asked to identify presumptive TB cases and refer them to the public-sector for diagnosis and treatment.[16–21] However, implementing various referral-based approaches has not been successful at a large scale, total TB case finding has remained much lower than the estimated levels, and private-providers treated more patients than RNTCP.[9,22,23] The lack of effective engagement of private-providers meant that a very large part of India's TB burden remained outside accountable treatment at par with the Standards for TB Care in India (STCI).[24] Recognising the critical role of private-provider engagement, RNTCP included the concept of an interface agency for engaging providers at scale in the National Strategic Plan for TB Control, 2012–2017. To develop and pilot this vision, the RNTCP engaged partners (Box1) and designed the Private Provider Interface Agency (PPIA) in Mumbai. PPIA was different from earlier referral-based engagement models for the following reasons – (1) it was led by the private-sector unlike RNTCP-led projects, (2) it directly financed the private-sector unlike RNTCP-funded programs or donor funds routed through RNTCP, (3) it engaged the informal providers in a formal project, and (4) it experimented with new diagnostic algorithms and allowed private practitioners to prescribe drug regimens other than the RNTCP regimens. We report the PPIA model and its achievement in first three and a half years of its implementation.

2. Methods

2.1. *Setting and context*

Mumbai is densely populated city, with nearly 21.3 million population in just 60 square kilometres. Nearly 60% of the population lives in slums.[25] The city has 171 government hospitals/dispensaries, which is far too less to meet the need of the population; however, a large private health sector has emerged, but with limited reliable data available on service provider numbers.[26] The city has historically reported exceptionally high number of TB notifications, largely from public health services, averaging roughly 30,000 TB cases annually. Mumbai's TB burden has never been comprehensively quantified, but is believed to be disproportionately high based on local studies, population conditions, and disproportionately high TB notifications from limited public services. For example, Mumbai accounts for 22% of notified TB cases in Maharahstra while housing only 12% of the state's population.[27] Mumbai also reports alarming instances of anti-TB drug resistance; with local, non-representative studies suggesting that 60% of patients without any previous history of TB were resistant to at least one drug, including 30% cases of rifampicin-resistant TB.[28] Extensively drug-resistant (XDR) TB has also been reported, which has led to increased political will to control the TB situation in Mumbai.[29–33] In 2013, as a result of wide media coverage on XDR TB in Mumbai, the Municipal Corporation of Greater Mumbai (MCGM) launched the "Mumbai Mission for TB Control", which included private-provider engagement as a central activity.[34] In 2014, PPIA was established by RNTCP and the MCGM, operated by PATH.

Box 1
Operational definitions of terminologies used in the manuscript.

Terminology	Definition
Development and implementation partners	Development and implementation partners included, and are not limited to, RNTCP's Central TB Division, the Municipal Corporation of Greater Mumbai, The Office of the World Health Organization Representative to India, the India liaison office of PATH (Seattle, WA), the Bill & Melinda Gates Foundation (Seattle, USA). Development was initiated in coordination and in parallel with a very similar PPIA effort in Patna, Bihar, implemented by World Health Partners (New Delhi, India).
Allopathic doctor	A medical graduate with a minimum Bachelor's degree in Medicine and Surgery in modern medicine. Those who have masters and post-doctoral degrees in modern medicine were also included in this category.
Non-allopathic doctors	Any medical practitioners without a degree in modern medicine were included in this category. Providers with Indian system of medicine were also included in this category.
Mapped	Any provider practicing in the city of Mumbai, who was identified and enumerated in the list of health providers available with PPIA were considered to be "mapped".
Engaged	A provider who was signed for utilisation of PPIA services for notification and management of TB patients in the city of Mumbai was considered to be "engaged" for service provision.
Active	A provider who utilized at least one PPIA service in a reporting period was considered to be "active".
Presumptive TB	Any patient with symptoms suggestive of TB who is under consideration for evaluation of TB.
Microbiologically-confirmed TB	A diagnosed TB patient with a demonstrated presence of Mycobacterium TB. Sputum AFB, Xpert-TB, cultures, and LPA are considered microbiological tests.
Probable TB	A diagnosed TB patient with evidence suggestive of "active" TB disease without demonstrated "microbiological" evidence. This is also called "Clinical TB".
Drug resistant TB (DR-TB)	Microbiologically-confirmed TB patients with evidence of resistance to one or more conventionally used anti-TB drugs. In this paper, DR-TB is used for TB patients with rifampicin resistance with or without any other resistance.
Multi-drug resistant TB (MDR TB)	Microbiologically-confirmed TB patients with demonstrated resistance to at least rifampicin and isoniazid. But in convention, even rifampicin resistant TB patients are considered MDR TB.
Extensively Drug Resistant TB (XDR TB)	MDR TB patients with demonstrated resistance to fluoroquinolones and any injectable second line anti-TB drugs.
Pulmonary TB	TB affecting the lungs tissue. Any microbiological evidence of TB in the sputum or clinical TB in the lungs with or without the presence of the disease elsewhere is considered a case of pulmonary TB.
Extra-pulmonary TB	TB affecting any parts of the body other than lungs is said to be extra-pulmonary TB. If a patient shows the presence of TB in the lungs along with sites other than lungs, he considered a case of pulmonary TB.
Pediatric TB	TB patients under the age of 15 are considered to be cases of pediatric TB.
Death	A TB patient who dies while on anti-TB treatment due to any reason is considered to have died due to TB for the purpose of outcome.
Successful treatment completion	A TB patient who consumes all the doses of anti-TB dugs as per the schedule prescribed by the treatment provider without interrupting treatment for a duration exceeding two months is considered to be a case of successful treatment completion.
Lost to follow up	A TB patient who interrupts treatment for a duration exceeding two months is considered to be "lost to follow up" for outcome purpose.
Xpert MTB/RIF	Molecular Cartridge Based Nucleic Acid Amplification Technology using Computerised GeneXpert Machines. This technology detects Mycobacterium TB along with rifampicin resistance status.

Table 1 – Services deployed by PPIA, Mumbai, India 2014–2017.

Services	Description	Remarks
1. Service to providers		
1.1 Continued Medical Education (CMEs)	Regular CMEs to the providers on updated information in TB diagnosis and management, including Standards for TB Care in India.	Free for providers. WHO consultants, high-value providers, program managers and opinion leaders were used for service delivery.
1.2 Regular reminders	Providers were regularly visited by PPIA staff for intermittent reminders and for behavioural change communication.	Free for providers
1.3 Help for notification	High volume networked providers were given assistance in notifying TB cases through human resource made available via subcontracted community NGOs.	Free to high-value providers
1.4 Specimen transportation	Hub hospital without an Xpert-TB test available the attached laboratory were given assistance to transport specimen to the testing networked laboratory.	Need-based free daily specimen transportation from the collection point to testing lab
2. Diagnostic facilities		
2.1 Chest X-ray	All the providers were allowed to offer FREE chest X-ray for evaluation of a presumptive TB patient.	X-ray providers were reimbursed using the e-voucher mechanism.
2.2 X-pert MTB	Hub centers and all the allopathic doctors were allowed to offer FREE X-pert MTB tests for evaluation of presumptive TB patients.	Testing laboratories were reimbursed using the e-voucher mechanism.
3. Drugs		
3.1 Anti-TB drugs	All allopathic doctors were allowed to prescribe FREE anti-TB drugs to the diagnosed TB patients in line with STCI through networked chemists.	Networked chemists were reimbursed drug using the e-voucher mechanism.
4. Call Center		
4.1 e-health platform as call center	An e-health platform was employed to register identified presumptive TB patients and to follow through to capture subsequent events till their outcomes. This platform was also used to verify e-vouchers at all stages and to facilitate financial reimbursements.	Toll free for providers and patients.
5. Adherence support to the patients		
5.1 Call center-based support system	Pill consumption pattern, identification of patients missing pills, periodical SMS reminders, voice calls, e-counseling services were provided through call center.	e-health platform
5.2 Adherence support through home visits	A cadre of dedicated human resource was used to regularly visit the patients at home to examine the pill consumption pattern, contact evaluation, creating awareness on cough hygiene, and to provide counseling to patients interrupting treatment.	Via subcontracted community NGOs

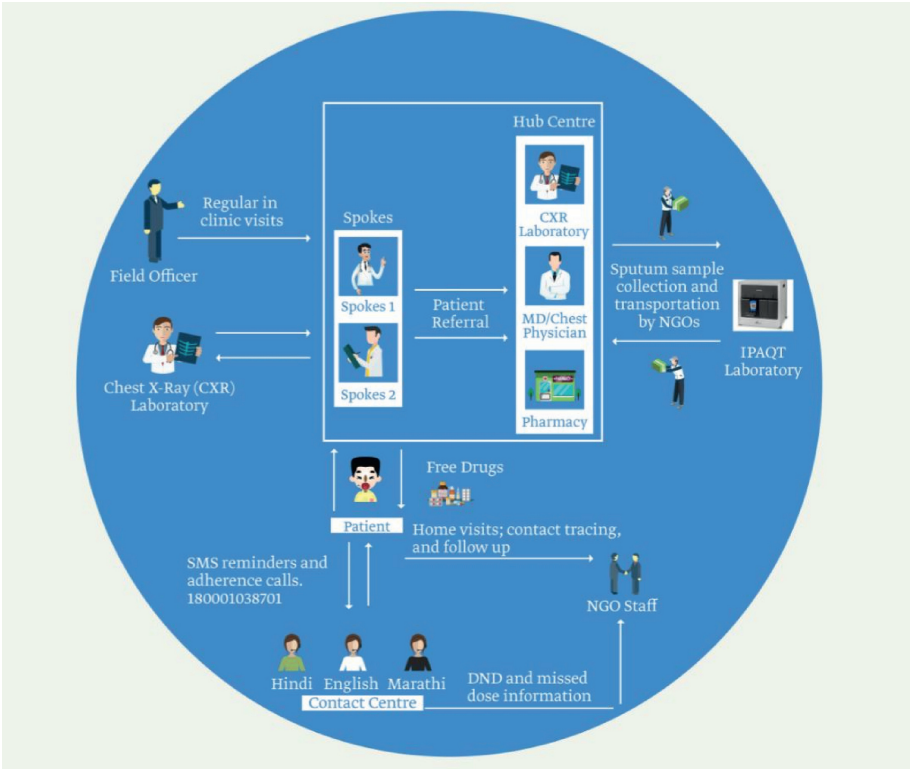


Fig. 1 – Service delivery model of PPIA services, relative to 'Hub' and 'Spoke' providers. Spokes are non-allopathic doctors who feed patients (after screening verbally or through x-ray) to hubs or allopathic doctors, who diagnose, notify, and treat the patients. Field officers offered low-intensity, high frequency in-clinic sensitizations to keep the doctors motivated. NGO staff helped patients in sputum collection and transportation to the laboratory. All the services were linked to contact center for patient event information management and re-imbursement of diagnostic test and drugs. Call center generated SMSs, mobile call-based tracking of doses consumed, and the home visits by NGOs helped adherence to the treatment. PPIA: Private-provider Interface Agency; NGO: nongovernmental organisation; CXR: chest x-ray; SMS: short message service; IPAQT: Initiative for Promoting Affordable and Quality TB Tests.

2.2. *Evaluation*

We conducted a descriptive analysis of the PPIA program implementation data collected from September 2014 to December 2017 in Mumbai. Data sources included the MCGM, RNTCP, and PPIA program data.

2.3. *Definitions*

Operational definitions of terms used in the manuscript are given in Box 1.

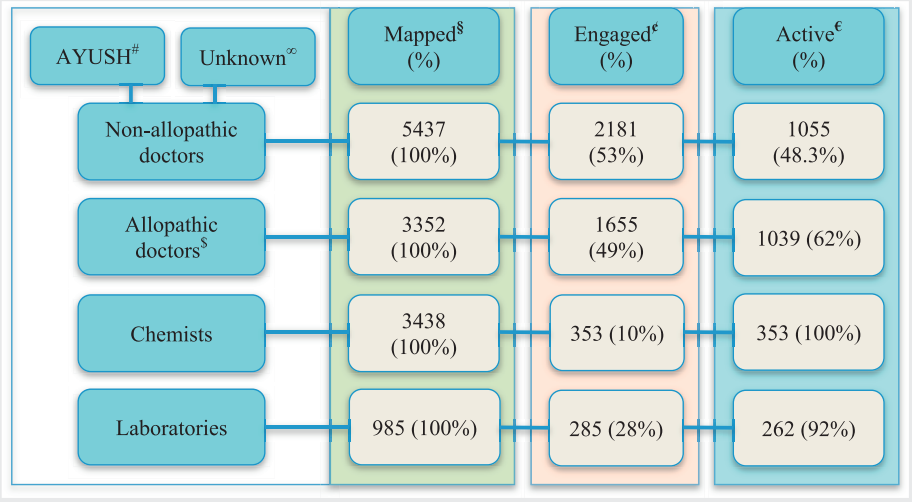
2.4. *The PPIA intervention*

The PPIA engaged private health providers, laboratories, and chemists into a referral network; extended essential TB support services; and monitored patients' cascade of care through diagnosis, notification, treatment initiation, and completion. Services provided by PPIA are indicated in Table 1.

Patients were provided free RNTCP-endorsed TB diagnostics (X-ray, Xpert MTB/RIF with sputum transportation services) and free anti-TB drugs. These services were issued to patients on providers' requests via electronic-vouchers (e-vouchers). The e-vouchers created a unique ID for each diagnostic or treatment service availed and sent an electronic reimbursement to the private laboratories and chemist against each ID upon verification. No direct financial incentives were given to the providers for any service.

The first step to initiate PPIA is to create a provider network. PPIA conducted a baseline analysis by mapping private-providers across the city including specialists, general practitioners, chemists, and diagnostic centres. A "hub and spoke" model was developed to monitor the nodes of service delivery along the care cascade, where general practitioners (spokes) referred cases to the specialist clinics (hubs). In order to optimize patient coverage, the PPIA intervention prioritized private-providers who were known to diagnose and treat large numbers of TB cases, as indicated by the situation analysis combined with field observation. Within the PPIA service delivery model, field officers acted as marketing agents and relationship managers for the various private-providers to ensure optimal uptake of PPIA services. Community NGOs were engaged and monitored by the field officers to support sputum transportation, monitor treatment adherence, and facilitate reporting. In hub hospitals and clinics which had a high patient load, the NGO staff were subcontracted to operate as in-clinic service coordinators.

Table 2 – Details of private health provider mapping and engagement under the Mumbai PPIA, and subsequent participation in PPIA services, 2014–2017.



$ Allopathic Doctors: Doctors with modern system of medicine, registered under Indian Medical Council.
# AYUSH: Health providers with Indian system of Medicine - Ayurveda, Yoga, Unani, Siddha, and Homeopathic.
∞ Unknown: Health providers with a qualification or degree which is not identified in India or without any known accreditation.
§ Mapped: Number of providers identified and line-listed by the PPIA staff as denominators for inclusion under the initiative.
¢ Engaged: Number of providers formally signed memorandum of understanding for inclusion in the initiative.
€ Active: Active is defined as utilization of at least one service during the reporting period.

The various services offered to providers were consistent with the STCI. Under PPIA, non-allopathic doctors screened presumptive TB cases verbally or by X-ray and referred them to allopathic doctors, who initiated diagnosis and TB notification. The program prioritized upfront use of Xpert MTB/RIF to microbiologically confirm TB and simultaneous drug susceptibility testing. Uptake of Xpert-MTB/RIF was restricted to specialists. Rapid screening for rifampicin resistance was prioritized due to the severe DR-TB epidemic in Mumbai. Upon diagnosis, TB cases were notified through calls to a PPIA-run call center. An e-health platform was used to capture patients' care cascade with demographic information, diagnostic and treatment details, adherence information, and outcomes for each case of TB.

It was PPIA's responsibility to supervise quality of care for privately-treated TB patients. Upon notification, a community NGO representative visited the patients' home to verify patient information and the services availed, and provided counseling on family Direct Observation of Treatment (DOT). Routine follow-ups were conducted by the NGO staff to monitor adherence and manage adverse reactions and gaps in treatment support. The PPIA service delivery model is captured in Fig. 1.

The effectiveness of the program is analysed in terms of increase in, 1) uptake of microbiological test, 2) presumptive TB identification and testing rate, 3) TB case notification rate among private-sector and as a whole, 4) proportion of pediatric patients evaluated, 5) treatment success rate among private-sector notified cases.

The number of TB patients treated in the private-sector was estimated by a pharmacy surveillance of private anti-TB drugs sales in Mumbai district, done by a third-party agency that has conducted similar market assessments on a national scale.[35] PPIA estimated the same metric by the number of 30-day (patient-month) drug e-vouchers validated by pharmacies engaged in the program. The proportion of PPIA drug sale among overall drug sales in the market was assessed as a proxy marker for patient coverage by PPIA in the city.

3. Findings

3.1. *Provider engagement*

Table 2 summarises results of the mapping exercise. Overall, program identified 5437 non-allopathic doctors, 3352 allopathic doctors (which includes 130 chest specialists), 3438 chemists, and 985 laboratories. Based on priority matrix, over half of all doctors, one-third of all laboratories, and nearly 10% of all chemists were formally engaged by PPIA. Among doctors who were engaged, 1055 (48%) non-allopathic doctors referred at least one presumptive TB patient and 1039 (62.8%) allopathic doctors notified at least one case throughout the reporting period.

3.2. *Overview of the evaluation*

Overall, 185,897 presumptive TB patients were identified and given slips for tests (Fig. 2). Of them, 140,602 (76%) underwent at least one diagnostic test, of which, 55,161 (39%) were Xpert MTB/RIF evaluations. Among 60,366 TB patients notified by PPIA, 43,604 (72%) were diagnosed under the program. Among

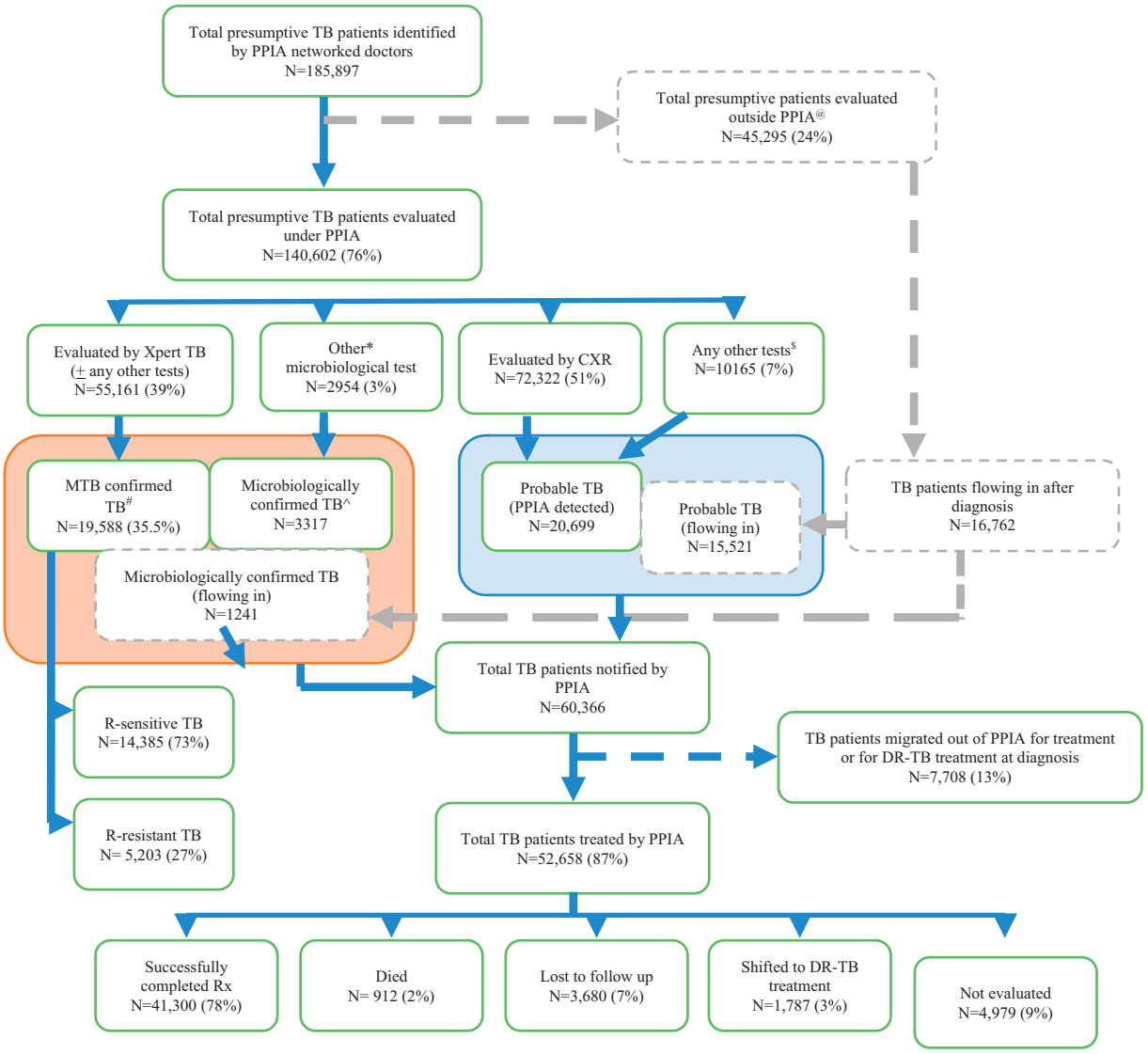


Fig. 2 – Overview of PPIA implementation data, Mumbai, India, 2014–2017. PPIA: Private-provider Interface Agency, @: Presumptive TB patients identified by networked providers but evaluated in laboratories not networked by PPIA, TB: Tuberculosis, Xpert TB: Cartridge Based Nucleic Acid Amplification Test, * Other microbiological tests include sputum AFB/ Culture DST etc, CXR: Chest X-Ray, $ any other tests include montox test/ESR etc., # MTB confirmed: Xpert TB results with confirmed mycobacterium TB. ^: Microbiologically confirmed TB by tests other than Xpert TB, R sensitive: Rifampicin sensitive, R resistant: Rifampicin resistant, Rx: Treatment, DR-TB: Drug resistant TB.

52,658 TB patients treated in the PPIA program, 41,300 (78%) completed the treatment successfully.

3.3. *Evaluation of presumptive TB patients*

The presumptive TB notification rate touched 666 per 100,000 in Q4 of 2017, i.e., nearly one in 150 residents of Mumbai were being evaluated for TB by private-providers using PPIA-supported diagnostic services each year (Fig. 3). While four wards identified more than 1000 presumptive TB patients per 100,000 population per annum on average, five wards identified less than 250 per 100,000 per annum (data not shown).

Pediatric patients (<15 years of age) represented a substantial part of those evaluated for TB. Among the 185,897 presumptive TB patients, 23,230 (12%) belonged to the paediatric age group. Of the total presumptive TB patients identified, the proportion of pediatric presumptive TB patients increased from 6% to 12% during the implementation period.

3.4. *TB notifications*

From 2014 to 2017, PPIA notified and brought 60,366 TB cases under surveillance. The annual number of TB case notifications in Mumbai increased by 58% from 34,794 in 2013 (prior to PPIA) to 54,906 in 2017 (Table 3). By 2017, among the 54,906 TB cases notified in MCGM, PPIA Mumbai accounted for 22,265 (41%). The annual case notification rate (CNR) per 100,000 population increased from 272 in 2013 (before the program) to 416 in 2017 (Fig. 4).

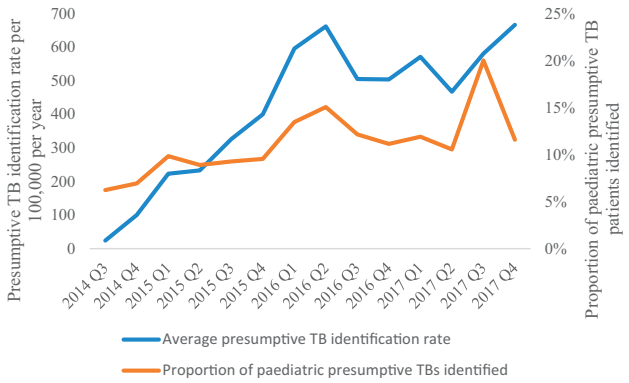


Fig. 3 – Trend of annual presumptive TB identification rate in PPIA per 100,000 population and the proportion of paediatric presumptive TB patients, Mumbai, India, 2014–2017. PPIA: Private-provider Interface Agency; TB = Tuberculosis. X-axes denotes year followed by quarter number; Q1 = January–March; Q2 = April–June; Q3 = July–September; Q4 = October–December. Average presumptive TB identification rate is the PPIA average in all implementing wards. All presumptive TB patients below the age of 15 years were considered paediatric.

Among 60,366 TB patients notified in three and a half years of implementation, 4497 (7%) were in the age group of 0–14 years, 29,937 (50%) were males, 24,146 (40%) were confirmed microbiologically, 5203 (9%) were Rifampicin-resistant (R-resistant), and 52,994 (88%) were pulmonary TB patients. Of the 19,588 TB patients diagnosed by Xpert MTB/RIF, 5203 (26.6%) were R-resistant (Table 4).

Cumulatively, of the 1039 doctors who notified cases, 125 (12%) contributed 80% (48,293 of 60,366) of the notified TB patients during the entire reporting period (Fig. 5). An additional 97 (9%) doctors contributed the next one-tenth of TB notifications, but these providers were often less consistent with their TB notification activities.

3.5. *Patient coverage*

Based on a third party evaluation, it was estimated that 16,190 TB patients were treated in the private-sector in September 2017.[35] In the same month, PPIA disbursed 10,449 patient-months of free anti-TB drugs, which is 65% private patient coverage (Fig. 6).

Table 3 – Trend of annual TB notifications by public and private-sectors, Mumbai, India, 2013–2017.

Year	Total TB cases notified by public	Total TB cases notified by PPIA only	Total TB cases Notified by Private (including PPIA)	Total TB case notifications (public + private PPIA)	Annual public CNR per 100,000	Annual private CNR per 100,000	Total district annual CNR per 100,000
2013	31,903	0	2891	34,794	249.05	22.57	271.62
2014	30,851	1679	7253	38,104	239.16	56.22	295.38
2015	27,200	13,577	18,134	45,334	209.18	139.46	348.64
2016	22,367	22,845	23,775	46,142	170.65	181.39	352.03
2017	25,179	22,265	29,727	54,906	190.58	225.00	415.57
Total	137,500	60,366	81,780	219,280			

PPIA: Private-provider Interface Agency; CNR: Case Notification Rate; TB: Tuberculosis.

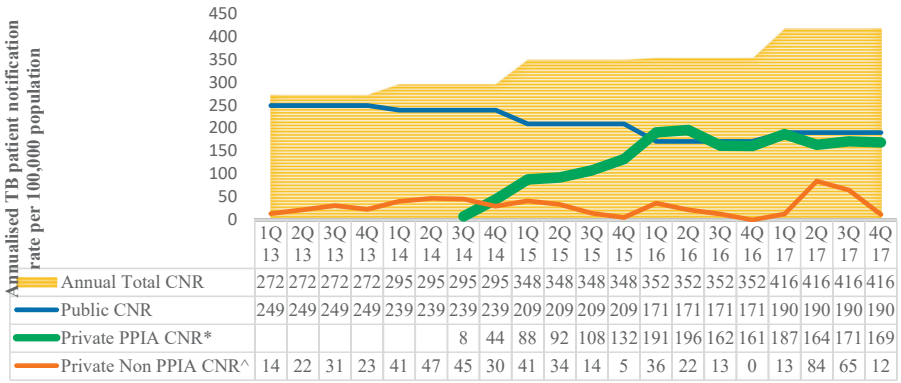


Fig. 4 – Trend of annual TB notification rate in PPIA per 100,000 population, Mumbai, India, 2014–2017. X axes: 1Q(year) signifies Jan–Mar(year); 2Q(year) signifies Apr–Jun(year); 3Q(year) signifies Jul–Sep(year); 4Q(year) signifies Oct–Dec(year). Public notification: Tuberculosis case notification to the National TB Programme by the public -sector health facilities. Private notification non-PPIA^: Tuberculosis case notification to the National TB Programme by the private-sector health facilities other than those enrolled in the PPIA initiative. Private notification PPIA*: Tuberculosis case notification to the National TB Programme by the private-sector health facilities enrolled in the PPIA initiative.

Table 4 – Demographic and clinical characteristics of notified TB patients, PPIA Mumbai, India, 2014–2017.

Characteristics	Numbers	Proportion	(95% CI)[b]
Age group of notified TB cases	**60,366**	**100%**	
0–14 years	4497	7.4%	(7.2–7.6)
15–24 years	20,731	34.3%	(33.9–34.7)
25–34 years	14,111	23.4%	(23.0–23.7)
35–44 years	7990	13.2%	(12.9–13.5)
45–54 years	6375	10.6%	(10.3–10.8)
55–64 years	4027	6.7%	(6.5–6.9)
65 years & above	2635	4.4%	(4.2–4.5)
Gender of notified TB cases	**60,366**	**100%**	
Male	29,937	49.6%	(49.2–50.0)
Female	30,424	50.4%	(50.0–50.8)
Transgender	5	0.0%	(0.0–0.0)
Microbiological confirmation			
Total cases notified	**60,366**	**100%**	
Microbiologically-confirmed	24,146	40.0%	(39.6–40.4)
Probable	36,220	60.0%	(59.6–60.4)
Drug resistance[a]			
Total Xpert-TB evaluations[a]	**55,161**	**100%**	
MTB detected	19,588	35.5%	(35.1–35.9)
R-sensitive[c]	14,385	73.4%	(72.8–74.0)
R-resistant[d]	5203	26.6%	(25.9–27.2)
Type of TB			
Pulmonary	52,994	87.8%	(87.5–88.0)
Extra-Pulmonary	7372	12.2%	(11.9–12.5)

[a] Xpert-TB: Cartridge based Nucleic Acid Amplification test named as Xpert-TB.
[b] 95% CI: 95% Confidence Interval with Wilson's score. There were 19,720 TB patients notified by PPIA during this period. Of them, 2698 had moved out of intervention before initiation of adherence support. Hence, eligible patients for outcome reported in the table did not involve these moved out patients. MTB: Mycobacterium Tuberculosis.
[c] R-sensitive: Rifampicin sensitive (proportions out of MTB detected).
[d] R-resistant: Rifampicin resistant (proportion out of MTB detected).

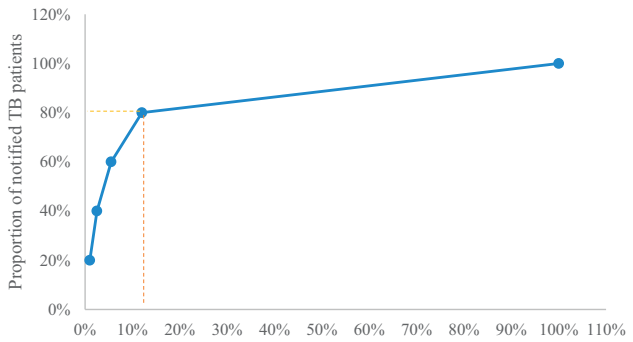


Fig. 5 – Contributions of private-providers to notification, PPIA, Mumbai, India, 2014–2017. PPIA: Private-provider Interface Agency. *calculation was based on the cumulative proportion of cases contributed by the individual doctors during the entire reporting period.

3.6. *Microbiological testing*

Among 60,366 PPIA-notified TB patients, 24,146 (40%) were microbiologically confirmed. Additionally, microbiological testing across pulmonary cases improved over time in PPIA from 32% to 51% (Fig. 7). Microbiological confirmation across pulmonary cases increased from 38% to 43% over the same period. Microbiological test positivity, defined as the proportion of cases microbiologically confirmed out of only those tested, improved from 29% to 37%. The proportion of pulmonary cases receiving a Drug Susceptibility Testing (DST) with Xpert MTB/RIF increased from 21% to 49% (Fig. 7).

3.7. *Treatment outcomes*

Table 5 shows a split of various treatment outcomes from 2014 to 2017. Of 60,366 TB patients notified during this period, 52,658 (87.2%) patients were treated under the program. Among patients treated under PPIA, 41,300 (78%) successfully completed the treatment. Of notified patients, 7708 (12.8%) migrated out for either DR-TB treatment at diagnosis (5,203) or treatment of TB outside PPIA (2,505), and 4979 (9%) could not be evaluated for outcome.

4. Discussion

To the authors' knowledge, this is the first report to describe a PPIA program in India. The program observed several important findings. First, the program showed that through a strategized approach, practicing for-profit private-providers can be optimally engaged in a public health program. Second, during the implementation of the program, TB notification from Mumbai increased by one and half times. Third, Xpert MTB/RIF was offered upfront to evaluate presumptive TB patients and the program provided universal DST for all. Fourth, the program observed an increasing uptake of microbiological testing during implementation. Fifth, only a small number of practicing providers contributed to majority of the TB notification. Sixth, the program observed a reasonably high level of treatment success in private-sector.

PPIA differed from earlier referral-based engagement models in terms of studying the network dynamics before the roll out. The initial mapping exercise helped to access provider behaviours, TB patient load, and networking with other service providers. This exercise, we believe, was important and provided relevant information for successful engagement and networking of the providers. PPIA program in Mumbai was designed and deployed in a private-sector ecosystem while preserving business relations between the labs, chemists, and providers. Unlike the earlier referral-based engagement models, PPIA gave the private-providers opportunity to manage TB patients within the broader ambit of STCI. Although, earlier referral-based engagement models had engaged with certain categories of private-providers, these had failed to engage individual providers to the scale comparable to PPIA.[22,36] In addition, the quantum of notification of TB patients by the program was unmatched to any previous referral-based models in India.[37] The recruitment criteria to engage providers and deployment of an exclusive behavioral

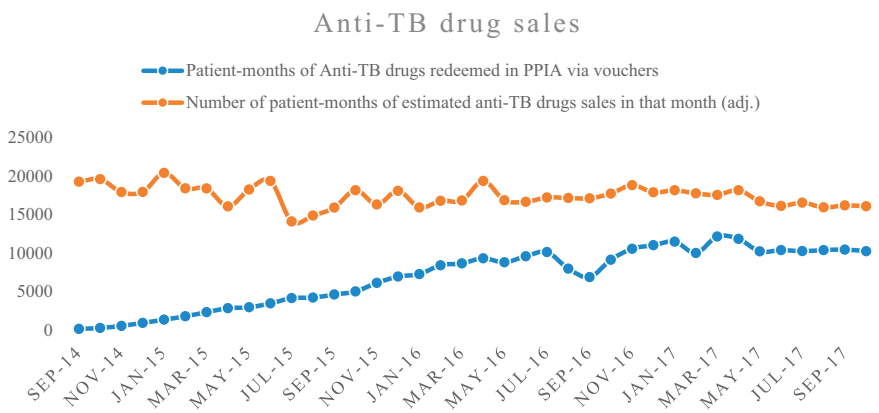


Fig. 6 – Total patient-months of anti-TB drug sales in private-sector and patient-months of anti-TB drugs for which free TB drug e-Vouchers were redeemed, Mumbai, May 2014–June 2016. PPIA: Private-provider Interface Agency; TB: Tuberculosis; Adj: Adjusted.

change communication (BCC) team of pharma-marketing specialists to keep the networked doctors motivated were believed to be crucial in this achievement. The BCC team adopted marketing techniques including relation-building and "low–intensity, high frequency" sensitization in the clinics for its success.

Early detection of all forms of TB including DR-TB is crucial in efforts to eliminate TB. A recent study emphasizes on the importance of using DST upfront for diagnosis and treatment of TB.[38] Upfront Xpert MTB/RIF evaluations of presumptive TB patients was an exclusive feature of the PPIA model in Mumbai. This novel feature resulted in early detection of a huge number of DR-TB patients and paediatric TB in the beginning, which otherwise would have been detected much later.

A third party pharmacy surveillance confirmed that the program covered two-thirds of the TB patients estimated to be treated in the private-sector in a span of three years. Wide patient coverage can be achieved in two ways; first, high-value providers identified and engaged appropriately in a sustained manner to increase patient base, second, the patients followed up to keep adherence optimal to cover all monthly refills increasing drug distribution volume. Focussed and strategized approach in selection of providers, use of e-platforms for follow up of patients on treatment, hassle free e-voucher mechanisms for quality assured drug refills might have contributed to this successful market capture by PPIA program.

A global meta-analysis showed that the likelihood of TB patients not completing the treatment in private facilities is two times higher as compared to public health facilities.[39] Contrary to this speculation, the successful treatment outcomes in Mumbai's PPIA program were quite high and comparable to Public-sector DOTS treatment outcomes. Among existing models for engaging private-sector, only few countries showed desirable levels of successful treatment

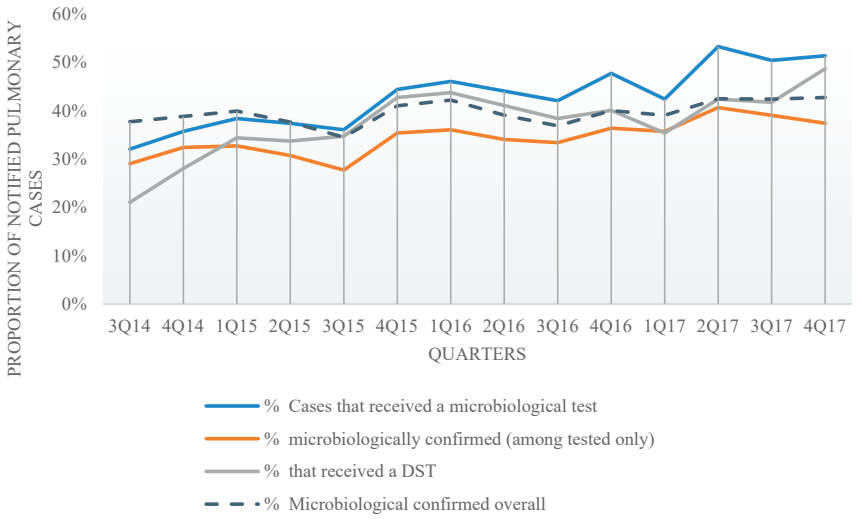


Fig. 7 – Quarterly proportion of notified pulmonary TB patients who received a microbiological test and proportion with positive microbiological test results, Mumbai, India 2014–2017. DST: Drug Susceptibility Test.

Table 5 – Trends of outcomes of TB cases notified by PPIA, Mumbai, India, Q3 2014 to Q3 2016.

Quarter-Year[a]	Total TB cases notified (a)	Migrated out of PPIA[f] (b)	Total TB cases eligible for outcomes (c = a-b)	Treatment outcome				
				Successfully completed treatment[b]	Died[c]	Lost to follow up[d]	Treatment regimen change[e]	Not evaluated[g]
				n (%)	n (%)	n (%)	n (%)	n (%)
2014	1679	195	1484	1094 (74)	25 (2)	142 (10)	63 (4)	160 (11)
2015	13,577	1840	11,737	8822 (75)	230 (2)	675 (6)	358 (3)	1652 (14)
2016	22,850	3161	19,689	15,813 (80)	436 (2)	863 (4)	853 (4)	1724 (9)
2017	22,260	2512	19,748	15,571 (79)	221 (1)	2000 (10)	513 (3)	1443 (7)
Total	60,366	7708	52,658	41,300 (78)	912 (2)	3680 (7)	1787 (3)	4979 (9)

[a] Quarter-Year: 1Q(year) signifies Jan–Mar(year); 2Q(year) signifies Apr–Jun(year); 3Q(year) signifies Jul–Sep(year); 4Q(year) signifies Oct–Dec(year).
[b] Successfully treated: Tuberculosis patients either cured with a microbiological confirmation at the end or who completed the treatment as per the treatment guidelines.
[c] Died: tuberculosis patients who died due to any cause during the treatment.
[d] Lost to follow up: Tuberculosis patients who discontinued treatment for more than two months for any reason.
[e] Treatment Regimen change: TB patients who were shifted to DR-TB treatment during the course of treatment due to change in DST pattern.
[f] Migrated out of PPIA: Tuberculosis patients migrated out of the program for DR-TB treatment or treatment for sensitive TB outside PPIA soon after notification.
[g] Not evaluated: Tuberculosis patients who could not be evaluated for outcome at the end of treatment for any reason.

outcome, that is, above 85%.[40] But these were referral-based engagement models where patients were being treated in the public-sector, hence, these outcomes can not be tagged to the private-sector. A study from Vietnam reported a success rate of 49% among TB patients treated in a semi-private set up with restricted autonomy.[41] The PPIA program in Mumbai showed that the desired outcomes can be obtained in un-restricted private-sector as well. Assumably, three-tier adherence mechanism (Call-center based support system, Adherence support through home visits, and treatment voucher tally) adopted in PPIA played an important role in this success. It also indicated that modern techniques can be used as an alternative to DOT without compromising much on the treatment outcome.

The PPIA program turned out to be a sought out solution for Universal Access to TB Care and to meet India's ambitious goal to eliminate TB. This program paved ways to streamline surveillance and standards of treatment in the private healthcare sector. Success of the PPIA program was also discussed at WHO global forums.[42] Consequently, the program is being scaled up across India as a part of the Joint Effort to End TB (JEET) initiative with support from the Global Fund. We believe that the program will have an impact on the Global TB Control efforts and can be scaled in other regions as well.

However, we observed certain limitations as well. The program data was initially captured manually and was later transferred to an ICT platform. The metadata set had hence certain challenges due to the availability of limited variables restricting the scope of analysis. The data had limitations inherent to secondary data. Initially, patients had to pay for for Xpert MTB/RIF, although made free later. This might have hindred its uptake in the beginning. The "for-profit" private-sector might have deterred to some extent by the program policy of "no direct incentives". This was supported by the fact that, despite efforts by the BCC team, many high-value providers failed to sustain their contributions. In PPIA program, a considerable number of patients were missed out for timely evaluation for various reasons, indicating a need for further refinement of the protocol for effective follow-up.

4.1. *Interpretation*

Tapping the private health-sector for a public health initiative is imperative to achieve universal health care in populous countries like India, with mixed healthcare market. The PPIA program in Mumbai demonstrated that private-providers can be effectively and comprehensively engaged for tuberculosis control in urban India. This experience has influenced national policy and has been adapted and funded for country-wide expansion. The model may also be considered to address public health issues where private-provider engagement can improve access and quality of care.

Funding and role of funders and technical assistance

PPIA in Mumbai was supported by a grant from the Bill & Melinda Gates Foundation (BMGF), and benefited from technical assistance from WHO. BMGF also provided technical assistance throughout the program. An initial patient pathway analysis was undertaken by FMR and Sambodhi, which mapped patients' touch points and preferences. McGill and The World Bank led the quality of care through standardized patients, which was helpful in provider selection and engagement. Andy McDowell undertook the qualitative study to fine tune the marketing strategy. The program also benefited from the operational modelling

inputs provided by the Indian School of Business and transmission modelling support from Imperial College, London.

Conflicts of interest

The authors have none to declare

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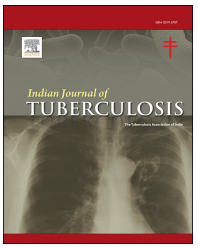

Original article

Lung Health Care pilot project trims patient pill load and antibiotic prescription in primary health care settings in Kerala, India

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ABSTRACT

Introduction: Kerala, the southern Indian state piloted Lung Health Care Project (LHCP) which is a locally adopted version of WHO recommended Practical Approach to Lung health (PAL). The current study assessed the impact of the project on the prescribing practices of doctors and consumption of antibiotics and other drugs.

Methods: This study compared performance of primary health care institutions with regard to drug prescriptions and consumptions before and after the implementation of the project. Chronic respiratory disease (CRD) patients in institutions implemented the project were interviewed in the OPD at exit and their prescriptions were documented at baseline and after six months. Focus group discussions were conducted with doctors to explore the reasons behind changes in drug consumption pattern.

Results: In the project implementing institutions, mean number of drugs prescribed for CRDs was 3.88 (SD 1.50) and 2.73 (SD 1.18) at baseline and after six months respectively ($p < 0.001$). Adjusted odds ratio for prescribing an antibiotic and injection to a CRD patient during impact assessment at institutions implementing project was 0.34 (95% CI 0.15–0.75 p 0.008) and 0.39 (95% CI 0.20–0.74 p 0.004) respectively, as compared to baseline. The factors which helped in reducing antibiotic and injection use as felt by the doctors were presence of a protocol, good quality trainings, supportive supervision and monitoring, availability of alternate drugs and good participation of staff nurses especially in-patient education.

Conclusion: Strict adherence to diagnostic and management algorithms of Lung health care project in a primary health care setting in India helped in reducing pill burden to patients and prescription of antibiotics and injections.

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1. Introduction

Respiratory diseases are among the leading causes of mortality and morbidity in developing countries.[1] Chronic Obstructive Pulmonary Disease (COPD) was the fourth leading cause of deaths in 2004, and is projected to become the third leading cause in 2030.[2] It has been estimated that 10–15% of all respiratory patients have Chronic Respiratory diseases (CRD).[3,4] CRDs, if not diagnosed, treated and managed correctly, pose problems for individuals and health systems alike. However, these facts have not much influenced the health demand and supply sides in addressing the issue effectively. CRD is viewed as a clinical problem of the individual. The socio-economic and public health aspects are often ignored.

In India, protocols are available for management of patients with respiratory illnesses in the academic circles and tertiary care centres. However, no definite protocol for their diagnosis and management is practiced at primary health care level, except for Tuberculosis. Prevalence of CRDs is higher in Kerala, the southern Indian state, compared to other states in the country, primarily attributed to the epidemiological transition with increasing older age group and shrinking younger age group.[5]

Despite having a low per capita income, Kerala state has achieved better material conditions of living with many of its indicators of social development comparable to those of developed countries. The state has a reasonably strong primary health care system with a good infrastructure of primary health centres.[6] To improve the quality of diagnosis, treatment and management of common chronic respiratory illnesses in primary healthcare settings, Government of Kerala has implemented a Lung Health Care (LHCP) pilot project which is a locally adopted version of WHO recommended Practical Approach to Lung health (PAL).[7,8]

Though PAL is a syndromic approach to the management of patients who attend primary health care services for respiratory symptoms, the locally adopted version for Kerala had a few basic clinical components since all Primary Health Centres (PHC) in Kerala are manned by qualified modern medicine practitioners.

LHCP has been piloted in 0.5 million population in Kollam district of Kerala. Of the 70 primary health care institutions in the district that cater to a population of 2.6 million, 16 institutions were selected for the project implementation to represent the state scenario in terms of geography and health care delivery. Average daily OPD attendance of these institutions ranges from 120 to 300. Clinical care team include a doctor, staff nurse and pharmacists and the field team has multipurpose health workers.

Standard steps of pilot implementation were followed from estimating the burden of CRDs, assessing the capabilities of the health infrastructure, developing and testing technical and operational guidelines, designing communication messages, formulating an information system, developing training materials and training of staff.[7,8] Customised and locally appropriate clinical algorithms were prepared for managing acute breathlessness, acute respiratory illnesses and CRDs. Local adaptation of PAL was characterised by training to primary care doctors to differentiate COPD and bronchial asthma, supply of Peak Expiratory Flow meters and training to staff nurses to record Peak Expiratory Flow Rate (PEFR), supply of inhaled medications and patient education to use inhaler devises, behaviour change communication for risk reduction, health system initiated domiciliary treatment adherence monitoring and interrupter retrieval. The pilot service delivery phase was for six months, from 12th May 2016 to 30th November 2016. A total number of 2100 CRD patients were registered and offered treatment during the pilot period.

At the beginning of the pilot, at least one doctor, a staff nurse, a pharmacist and a team of peripheral health workers were there in all primary care institutions of Kollam district. All doctors had basic training in diagnosing and treating COPD and Bronchial asthma. All staff nurses had basic training in injections through intravenous and intramuscular routes, administration of inhaled salbutamol and ipratropium through nebulizer, all pharmacists had basic training in dispensing drugs and educating patients on the doses, timing and duration of drugs. All institutions had sufficient stock of oral and injectable antibiotics and steroids, salbutamol and ipratropium respiratory solutions and nebulizer machines for their administration through respiratory route, oral salbutamol and theophylline. A general OPD register, a CRD patient register, a drug stock register, drug issue registers and injection registers were the standard documents in all institutions. PAL institutions were additionally provided with salbutamol and beclomethasone combination dry powder capsules for domiciliary management of stable asthma, levosalbutamol and ipratropium dry powder capsules for domiciliary management of stable COPD and dry powder inhalation devices for domiciliary use of patients and Peak flow meters for assessing PEFR of patients. Doctors and staff in the project implementing institutions were trained in locally adapted TOG of PAL.

Many country experiences have shown that PAL strategy had helped in decreasing drug prescriptions particularly antibiotics and improving the quality of drug prescription for CRD patients.[9–11]Through this study, we aimed to assess the impact of the Lung health care project on the consumption of CRD drugs and prescription practices.

2. Methods

To compare performance of the 16 pilot institutions, another 16 primary care institutions were selected randomly as controls from the remaining areas of Kollam. Monthly aggregate details of disbursement of injectable bronchodilators, steroids and individual type antibiotics were collected from stock, issue and injection registers from study institutions. Similar information was collected from all 32 institutions for the concurrent period in the previous year (May to November 2015), to account for any seasonality changes in the pattern of diseases or severity.

At baseline and at end of pilot, randomly selected CRD patients from all study institutions were interviewed and copies of their prescriptions were collected at OPD exit. Two focus group discussions (FGD) were conducted among doctors of the project implementing institutions to understand the reasons behind perceivable changes in the drug consumption

pattern. An FGD guide was developed and the key themes of the FGDs were a) how LHCP project affected the health system b) what, if any, are the lessons for the health system from LHCP project c) how will LHCP project affect the drug consumption patterns of primary health care institutions from your experiences, d) what LHCP project will do with doctor's prescribing practices e) what are the challenges to be expected in LHCP project implementation. Both the FGDs were moderated by the same person who was experienced in conducting FGDs. The moderator ensured that the themes were fully discussed and that all participants were given a chance to express their views fully. Six doctors participated in one FGD and four in the other. Each FGD lasted for around 40 minutes with additional 10–15 minutes for informal conversations. The proceedings were audiotaped with the consent of participants. Two researchers recorded the proceedings, noting key themes and monitoring verbal and non-verbal interactions.

Double data entry was done using Microsoft Excel and analysis was done using Statistical Package for Social Sciences version 15 (SPSS Inc., Chicago, IL, USA), for Microsoft Windows. The institution wise aggregate data of drugs were converted to number of tablets/injections consumed per 1000 OPD Visits and were compared using Wilcoxon-signed rank test. Logistic regression was done with prescription of antibiotics and prescription of injections as dependant variables and demographic characteristics as independent variables.

For qualitative study, the audio-tapes were transcribed verbatim. The team read the transcripts and notes and reached a consensus. Any disagreements were discussed regularly within the team to reach a consensus regarding theme coding. Sections with similar coding were grouped according to the predetermined themes. Repeated themes were marked as important in red font colour. All the flagged statements were put together and synthesized. Approval for the study was granted by the ethics committee of Travancore Medical College, Kollam.

3. Results

Average monthly total OPD visit per institutions was 4534 and average number of visits per month per institution with a diagnosis of acute respiratory tract infections was 947 and chronic respiratory disease was 194. A total of 94 and 100 CRD patients were interviewed at baseline and after six months in the LHCP project implementing institutions and 88 and 96 CRD patients were interviewed at the control institutions. The characteristics of the study subjects were shown in Table 1.

On analysing the prescriptions, the mean number of drugs prescribed for CRDs was 3.88 (SD 1.50) and 2.73 (SD 1.18) at the baseline and during the impact assessment surveys respectively, showing a mean decrease of 1.15 ($p < 0.001$); the mean decline at control group was 0.33 (p 0.184). In LHCP institutions, 39 (41.5%) CRD patient's prescriptions had an antibiotic at the baseline while 21 (21%) patient's prescription had the same during the impact assessment survey showing a 49.39% reduction (p 0.002). The reduction in antibiotic prescription in control institutions during the concurrent period was 13.4%. Injections (a bronchodilator and/or steroids) were prescribed for 37 (39.4%) CRD patients at baseline in the LHCP institutions, while 20 (20%) patients had the same after six months (p 0.002) showing a reduction of 49.24%. The control institutions showed a reduction of 13.4% (p 0.269). The results of exit interviews were shown in Table 2.

Logistic regression was done by entering injection prescribed as dependant variable and age, gender, diagnosis, Socio economic status (SES) and baseline or impact assessment survey as independent variables. Adjusted odds ratio for prescribing an injection to a CRD patient during impact assessment at LHCP implementing institutions was 0.39 (95% CI 0.20–0.74 p 0.004) as compared to baseline. Similarly, adjusted odds ratio for prescribing an antibiotic to a CRD patient at LHCP implementing institutions during impact assessment period was estimated to be 0.34 (95% CI 0.15–0.75 p 0.008) as compared to baseline.

On analysing the aggregate data regarding consumption of drugs at the institution level the following findings were noted. There was reduction in the use of oral antibiotics and injectable bronchodilators and steroids in the LHCP and control institutions. However, the reduction was much higher in LHCP institutions. Injectable theophylline, hydrocortisone, oral Ciprofloxacin, oral amoxicillin and oral amoxicillin-clavulanic acid combination showed a reduction in LHCP institutions that was 3.98, 9.80, 7.41, 4.63 and 1.70 times higher than that of the control institutions respectively. While injectable dexamethasone showed a reduction by 30.82% in

Table 1 – Characteristics of Subjects with Chronic Respiratory Diseases included in the exit interviews for baseline and impact assessment survey of Lung Health care pilot project, Kollam, Kerala.

Characteristics	Categories	LHCP implementing Institutions			Control Institutions		
		Baseline survey (n = 94)	Impact survey (n = 100)	P value	Baseline survey (n = 88)	Impact Survey (n = 96)	P value
Age	Mean (SD)	59.31 (16.70)	62.26 (12.94)	0.171	58.9 (15.69)	58.7 (18.02)	0.922
Gender	Male	42 (44.7%)	52 (52%)	0.191	44 (50%)	58 (60.4%)	0.102
	Female	52 (55.3%)	48 (48%)		44 (50%)	38 (39.6%)	
Socio-Economic Status	APL	32 (34%)	39 (39%)	0.285	28 (31.8%)	40 (41.7%)	0.109
	BPL	62 (66%)	61 (61%)		60 (68.2%)	56 (58.3%)	
Probable Diagnosis	COPD	60 (63.8%)	66 (66%)	0.620	54 (61.3%)	59 (61.4%)	0.984
	Bronchial Asthma	29 (30.9%)	26 (26%)		30 (34.1%)	33 (34.4%)	
	Others	5 (5.3%)	8 (8%)		4 (4.5%)	4 (4.2%)	

APL = Above Poverty Line, BPL = Below Poverty Line.

Table 2 – Impact of Lung Health Care Project on drug prescriptions for patients with chronic respiratory disease based on exit interviews.

Characteristics	LHCP implementing Institutions				Control Institutions			
	Baseline survey (n = 94)	Impact survey (n = 100)	P value	Difference	Baseline survey (n = 88)	Impact survey (n = 96)	P value	Difference
Mean (SD) number of drugs in the current prescription	3.88 (1.50)	2.73 (1.18)	<0.001	−1.15	3.52 (1.46)	3.18 (1.89)	0.184	−0.33
Number (%) of patients received an Injection during the visit	37 (39.4%)	20 (20%)	0.002	49.24% reduction	42 (47.7%)	369 (40.6%)	0.206	14.8% reduction
Number (%) patients received an antibiotic during the visit	39 (41.5%)	21 (21%)	0.002	49.39% reduction	36 (40.9%)	34 (35.4%)	0.269	13.4% reduction

LHCP institution, there was an increase by 10.05% in control institutions. The mean number of drugs and antibiotic tablets consumed per every 1000 outpatient department visits were consolidated in Table 3.

All the doctors participated in FGDs agreed that their behaviour in prescribing antibiotics and injections has changed positively because of LHCP, to varying extents. The prevailing feeling in both the FGDs were that LHCP gave them confidence and comfort in following protocols like repeating the nebulized respiratory salbutamol at 20 minutes interval instead of a single intravenous shot of theophylline and steroid, to manage acute breathlessness in the emergency room. Trainings have helped them in re-realising the importance of rational drug prescriptions and reducing prescriptions of ciprofloxacin and amoxicillin clavulanic acid. One doctor commented that he did not realise the huge consumption of antibiotics in his institution till it was presented during the review meeting. Three other doctors also agreed that the review of antibiotic consumption during LHCP review meetings helped them in changing their behaviour. They all recognised the role played by staff nurses in counselling patients who were dependant on injections. Some of the doctors commented that they started following the principles of LHCP protocol to diseases other than respiratory illness also. Doctors who do private practise agreed that the behaviour of rational prescriptions extended to their private practice also. Also they had a general opinion that the need for antibiotics reduced to some extent as patients experienced less infective exacerbations after LHCP implementation. The factors which helped in reducing antibiotic and injections as felt by the doctors were: a) Presence of a protocol, b) Good quality training, c) Supportive supervision and monitoring, d) Availability of alternate drugs especially inhalers and e) good participation of staff nurses especially in patient education. They felt that all doctors in the institutions need to be trained as trained doctor and non-trained doctor sitting together in an institution has sometimes resulted in conflicts of ideas. A few transcribed verbatim accounts of doctors were shown in Table 4.

4. Discussion

PAL intends to strengthen health systems response to respiratory diseases. Development and implementation of locally appropriate clinical guidelines for primary care settings and

Table 3 – Consumption of drugs in the peripheral health centres before and during LHCP pilot project, Kollam, Kerala.

	PAL Implementing Institutions				Control Institutions			
	Drugs consumed (Number)/1000 OPD Visits				Drugs consumed (Number)/1000 OPD Visits			
	Pre LHCP[a] Mean (SE)	During LHCP[b] Mean (SE)	p value	Percentage change	Pre LHCP[a] Mean (SE)	During LHCP[b] Mean (SE)	p value	Percentage Change
Injection Theophyllin	21.60 (7.92)	11.19 (5.87)	0.008	−48.19%	23.13 (6.64)	20.33 (3.90)	0.072	−12.10%
Injection Dexamethasone	25.79 (7.65)	17.84 (5.82)	0.007	−30.82%	23.38 (5.92)	25.73 (6.17)	0.550	+10.05
Injection Hydrocortisone	3.21 (1.73)	0.89 (0.39)	0.025	−72.27%	3.66 (1.62)	3.39 (1.70)	0.724	−7.37%
Amoxyxillin	1706.02 (200.11)	1399.01 (194.34)	0.047	−17.99%	1285.2 (180.1)	1235.31 (134.57)	0.188	−3.88%
Ampicillin	224.21 (165.26)	202.32 (141.05)	0.779	−9.76%	244.2 (89.3)	231.56 (114.8)	0.433	−5.17%
Ciprofloxacin	280.07 (44.65)	151.16 (38.97)	0.047	−46.02%	289.78 (55.89)	271.79 (78.93)	0.658	−6.20%
Doxycycline	288.90 (73.49)	244.00 (84.03)	0.037	−15.5%	322.62 (82.92)	308.73 (95.18)	0.322	−4.30%
Azithromycin	213.46 (34.26)	154.25 (32.91)	0.114	−27.71%	148.52 (23.19)	152.61 (24.51)	0.224	+2.75
Amoxycillin-clavulanic acid	211.33 (68.59)	159.29 (39.84)	0.037	−24.62%	225.06 (47.2)	192.46 (52.11)	0.181	−14.4%
Cefixime	29.04 (12.24)	39.85 (17.74)	0.333	+37.22%	18.52 (8.71)	36.51 (17.21)	0.101	+97.13%
Cefadroxil	77.42 (39.39)	63.58 (24.65)	0.767	−17.8%	79.28 (42.52)	67.34 (42.05)	0.525	−15.06%

[a] May–Nov 2015.
[b] May–Nov 2016.

Table 4 – Transcribed verbatim accounts from FGDs among doctors.

"Protocol was the major factor. It gave me confidence not to write unnecessary drugs. I think we should have protocols for all the disease conditions at primary health care level"
"I never realised that the problems of quinolone resistance is such a huge problem. It is good that the issue is included in the training sessions. Now I think twice before writing quinolone"
"Infective exacerbations among the patients reduced to a great extent. That is why antibiotic use came down"
"There used to have a long queue of COPD patients in the morning to get injections. It was difficult for the patients at first to abruptly stop injections. But with the help of nurses and good patient education we managed it. Now there is no such long queue"
" I am following the same line of management (LHCP) now in my private practice also"
"Even though they (patients) were demanding injections initially, they (patients) themselves are convinced now. They are happy now and are not asking for any more injections"
"I was prescribing less quinolone and injections prior to LHCP also. But now I have stopped it completely"
"I was shocked to see the antibiotic and injection consumption pattern of my institutions. I never realised it before. The projection of drug consumption pattern during review meeting might have definitely influenced the behaviour of doctors"
"The doctor sitting next to me is new and is not trained in PAL. The patient may go to him also, if I am not there. Then there will be conflict of ideas. Better train everybody on protocols"
"I used to write antibiotics for all mild or moderate exacerbations. Now I am convinced that antibiotic is not necessary in all cases. I could not find any difference when giving it and now not giving it"
"My only worry is that, if in case the supply of inhalers to PHCs stopped from Government side, how will I manage. Do I need to start writing injections again!"

building up of management support within the health system are essential for this. Experiences elsewhere show that PAL not only improves the quality of care of respiratory patients and improve the efficiency of health systems in managing respiratory cases, but also demonstrates improvements in other indicators of quality of health care.[8]

LHCP pilot project in Kerala has resulted in reduction in the prescription of antibiotics. This observation is consistent with experiences from other countries like Jordan, Kyrgyzstan, Syria and Bolivia where the decrease ranged between 11% and 27%.[8–11] Reduction was observed in all categories of respiratory conditions in Syria while it was mainly observed in patients with acute lower respiratory infections in Bolivia and chronic respiratory diseases patients in Algeria.[8–11] No difference in antibiotic use was reported in South Africa.[12] Our pilot project showed profound decrease in use of Ciprofloxacin (46%) and Amoxicillin Clavulanic Acid combination (25%). The reduction in aggregate consumption was validated by audit of individual prescriptions which showed disappearance of antibiotics in the prescription for approximately 50% of CRD patients. Locally adopted PAL protocol of Kerala emphasised to rule out TB and not to initiate fluoroquinolones for treating respiratory infections in the context of a relatively high resistance to quinolones among multi-drug resistant TB (MDRTB) cases in the State (unpublished). Staffs were alerted during the training against the widespread use of quinolones for treating common respiratory conditions. These factors are also cited as reasons for drastic fall in quinolone (Ciprofloxacine) use in the LHCP implementing area. The drop was also visible in consumption of other antibiotics that were commonly used for treating respiratory illnesses in the area like Azithromycin, Amoxycillin, and Doxycycline. The indications for initiating an antibiotic in acute and chronic respiratory conditions were clearly drafted in the LHCP Treatment and Operational Guidelines.

Reports show that antibiotic use increased several folds in India recently.[13] Indiscriminate and inappropriate use of antibiotics has been attributed to rapid increase and spread of ant-microbial resistance. Preventing and managing antimicrobial resistance is imperative as the presence of multidrug-resistant organisms has generated substantial apprehension among clinicians, public health experts and health system managers. Emergence of extreme forms of drug resistance has been a challenge to TB control in India. Quinolones, Amoxicilline Clavulanic acid combination are reserve drugs for extensively drug resistant TB (XDRTB) in RNTCP. Reduction in exposure to these drugs would preserve the effectiveness of the regimes containing them. LHCP may thus catalyse design of effective antibiotic policies on one hand and demonstrate models to implement the same on the other.

Prescribing injectable theophylline and dexamthasone for CRD patients was a common practice in the PHC setting in Kollam, as evidenced by the results of baseline exit interviews. It was the case irrespective of the severity and type of CRD. Respiratory salbutamol was being concurrently administered through nebulizers, but the relief of symptoms were attributed to the injections by patients resulting in a demand from the patients' side during every next exacerbation. During LHCP training sessions, doctors and staff nurses have attributed this to high demand from patients, quick relief of symptoms, ambiguity about repeated use of inhaled bronchodilators and ipratropium through nebulizers and popular belief that long use of inhaled medications for maintenance causes addiction. Inhalational medicines were not available in the PHCs before the roll out of LHCP. Oral salbutamol, theophylline and prednisolone were the available alternatives. The number of consumed injectable bronchodilators and steroids was one of the indicators in LHCP monthly reports and review meetings. Most of the institutions showed a steady decline in the number of those injections every month. Injection hydrocortisone was used to manage exacerbations in the PHCs before roll out of LHCP. The drastic reduction in the number of hydrocortisone injection at the LHCP implementing PHCs could be either due to a decrease in the exacerbations or due to strict adherence to LHCP protocol. Small decline in the number of Injectable bronchodilators were also seen in the control institutions which could be due to the "ripple" effect.

India contributes 25%–30% of the global injection load. A majority of curative injections in India were reported to be unnecessary and two third were found to be unsafe.[14] Unsafe injections account for 32% of new hepatitis B virus (HBV)

infections, 40% of new hepatitis C virus (HCV) infections and 5% of new HIV infections.[15]

The study was done as part of an implementation of a public health pilot project in a program setting and not planned as pure research. Many high-quality randomised controlled trials are often based on highly selected patients, but this study includes subjects who represent the population of patients seen in day-to-day practice in the primary health care setting of Kerala. We have taken possible steps to ensure the internal validity of the study and avoiding biases that would prevent comparability between the data sets of the baseline and impact surveys. However factors like season of study, differences in demographic characteristics, co-morbidity and severity of disease conditions would have confounded the results. 'Hawthorn effect' was likely to influence the prescribing practices, but aggregate data of drug consumption at institutions were also consistent with the exit interview findings. The effects studied were of a six months period only. Despite these limitations, the findings have many public health and policy implications.

The cost saved by health system due to the decrease in use of antibiotics and injections may balance the cost for scale up of LHCP. LHCP has taught that in places where guidelines and training are respected, change is possible. To summarise, LHCP pilot project in India implemented in an area with a reasonably sound primary health care system has proved that it promotes rational prescribing practices. We also believe that customisation of generic guidelines of PAL that is more of syndromic in nature to simple clinical management guidelines favoured the behavioural changes in the primary care setting of Kerala, which is invariably manned by qualified doctors.

Patients benefits resulted from the implementation of locally adopted PAL were, significant reduction in exacerbations, medical consultations and hospitalization. These benefits are the subject of a separate study by the authors.

Author contributions

SB and RPS formulated the study design. RPS, SB and KV were responsible for data acquisition and analysis. RPS and SB drafted the original manuscript. SA, JS, BG, MMS and SM made substantial contribution to the analysis and interpretation of data and revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Conflict of interest

We declare no conflict of interest.

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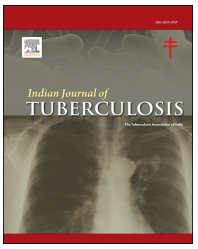

Original article

Awareness and perspectives on expansion of latent TB management among public-sector physicians and medical trainees in Delhi, India

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ABSTRACT

More than one in two healthcare workers (HCWs) in developing countries have latent tuberculosis infection (LTBI), an asymptomatic condition signifying persistent tubercular infection in absence of disease.

Objective: to evaluate the physician attitude towards LTBI preventive therapy and their perspectives regarding the potential expansion of latent TB management under the RNTCP.

Material and methods: We conducted a cross-sectional analysis among 60 participants of a continuing medical education program during October' 2019 in a medical college in Delhi, India.

Results: We enrolled a total of 30 medical officers, 15 resident doctors and 15 medical interns, comprising 27 (45%) males and 33 (55%) females. Only 9 (15%) participants were aware of existing RNTCP guidelines for programmatic management of LTBI. The median (IQR) self-rated willingness of the participants in receiving treatment for LTBI after confirmation of diagnosis on a 10 point continuous rating scale was 6 (5.8). The principal reason attributed to the treatment hesitancy were concerns over drug side effects 19 (31.7%), emergence of drug resistance 11 (18.3%) and the likelihood of reinfection 4 (6.7%). Support for expansion of preventive therapy among household TB contacts was varied, with maximum (41.2%) participants wanting it only for the comorbid patients.

Conclusion: LTBI preventive treatment is associated with considerable side effects and lack of long-term benefits by a majority of Indian physicians despite significant personal health concerns in treating pulmonary TB cases.

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1. Introduction

India accounts for one-fourth of the global burden of Tuberculosis (TB), which when combined with poor airborne infection control practices also results in a high latent TB infection (LTBI) (40–60%) burden.[1,2] The management of LTBI is a significant public challenge since it represents an enormous reservoir of asymptomatic but persistent tubercular infection. Almost one in ten LTBI cases are at risk of progression to TB disease during their lifetime with greater susceptibility amongst close-contacts of active TB cases and in those with an immunocompromised health status.[3]

It is well-established that healthcare workers (HCWs) are at increased risk of contracting occupational TB due to regular encounters with TB symptomatic cases, suboptimal implementation of guidelines for hospital airborne infection control and increased stress and burnout subject to a high workload.[4,5] A study among medical trainees at a tertiary care center in Pune, India reported a total of 26 (3.9%) TB disease cases among 662 medical trainees with an estimated disease incidence of 3279 cases/100,000 person-years.[6]

There is growing recognition of the high burden of LTBI in HCWs compared to other occupations, with the infection usually being acquired early during their period of training.[7,8] The prevalence of positive TST and IGRA in HCWs is estimated to be 50% and 39% respectively in low and middle-income countries.[9]

LTBI can be safely and effectively treated through preventive therapy using Isoniazid containing drug regimens.[1] Among HCWs, INH Preventive Therapy is estimated to reduce the lifetime risk of morbidity and mortality due to TB.[10] The World Health Organization (WHO) has therefore designated the treatment of LTBI as a key strategy for eliminating global TB and also advocate treating HCWs for occupational LTBI.[11] However, at present, the Revised National Tuberculosis Control Program (RNTCP) does not recommended LTBI treatment in any population except in children below 6 years of age and the PLHIV.[1]

Nevertheless, there exist a significant potential hesitancy in acceptance of treatment for LTBI when evaluated through the classical health belief model.[12] LTBI is an asymptomatic condition with absence of TB disease that reduces the perceived susceptibility. Moreover, concerns over side effects of drugs increases the perceived barriers while the apprehension over reinfection with LTBI in the persistently infectious clinical work environment can diminish the perceived benefits of LTBI treatment.

A comprehensive understanding of the extent of physician willingness to receive treatment for LTBI and identification of the knowledge and perception barriers that diminish its acceptability is important for safeguarding their health. Furthermore, securing the support and collaboration of the physicians responsible for implementation of the RNTCP is essential for any further programmatic expansion of LTBI management amongst household pulmonary TB contacts.[13] However, there is paucity of data exploring the awareness and acceptability of LTBI treatment in physicians employed in high-burden settings like that in India.

A training workshop on LTBI management strategies and the feasibility of expansion was conducted in a premier medical college in Delhi. We conducted this analysis of the training workshop with the objective of evaluating the physicians' attitude towards LTBI preventive therapy and their perspectives regarding the potential expansion of latent TB management under the RNTCP.

2. Methods

2.1. Study design and setting

We conducted a cross-sectional analysis amongst participants of a continuing medical education programme during October' 2019 in a government medical college in Delhi, India.

2.2. Study population

The participants included 30 medical officers nominated by the government of the national capital territory of Delhi, 15 resident doctors of the department of community medicine and 15 medical intern trainees affiliated to a premier medical college in Delhi.

2.3. Primary outcome

physician attitude towards the acceptability of treatment for LTBI and the programmatic expansion of LTBI management in India.

2.4. Secondary outcome

knowledge (epidemiology, diagnosis and treatment) of LTBI.

2.5. Methodology

Two CMEs were conducted in batches of around 30 participants each. Each CME had three sessions including a first lecture on epidemiology of latent TB, a second lecture on management of latent TB and a third session on brainstorming to explore participant attitudes and perceptions towards the prospective expansion of latent TB management under the RNTCP.

Data collection was conducted using a self-administered questionnaire. Knowledge and practices were ascertained through close ended multiple choice questions, while attitude questions were coded on a 10-item continuous rating scale.

2.6. Statistical analysis

We analyzed the data using IBM SPSS Version 25. We expressed the results in frequency and proportions for qualitative variables and mean and standard deviation for ordinal/continuous variables. Paired differences (pre-post analysis) were ascertained using the McNemar's test for categorical data, and the Wilcoxon Sign Rank test for continuous data. A P value < 0.05 was considered as statistically significant.

2.7. Ethics

The study was approved with exemption from full-review by the Institutional ethics committee, Maulana Azad Medical College & Associated Hospitals, New Delhi. Written and informed consent was obtained from all the participants.

3. Results

There were 27 (45%) male and 33 (55%) female (N = 60) participants. The mean (±SD) age of the participants was 31.5 (±8.3) years, ranging from 22 to 51 years. The median years of clinical experience of the participants was 7.5 years. In a typical month, nearly 1–10, 11–25, 26–40 and > 40 Tuberculosis (TB) patients were reportedly treated on outpatient basis by 36 (60%), 13 (21.7%), 4 (6.7%) and 7 (11.7%) participants respectively. A total of 10 (16.7%) participants also reported a personal history of receiving prior treatment for TB disease.

3.1. Awareness of TB elimination targets

A TB elimination target of 2025 has been adopted by the Indian government that was reported correctly by 37 (61.7%) patients. However, awareness of current annual rate of decline of TB incidence (25%) and the net rate of decline required to achieve TB elimination targets was low (30%).

3.2. Awareness on latent TB infection (LTBI)

Most participants (90%) had heard about LTBI prior to the training program. As per the RNTCP, only the people living with HIV (PLHIV) and children below 6 years of age are being provided INH Preventive Therapy (IPT). However, only 9 (15%) participants were aware about these existing strategies for programmatic management of LTBI in India. The global LTBI burden was correctly reported by a total of 20 (33.3%) participants but the awareness of higher LTBI burden in HCWs was significantly higher (61.7%). The knowledge about the current WHO recommendations for the diagnosis and treatment of LTBI was lacking in most participants. Nevertheless, the knowledge score of the participants significantly improved on post-test assessment after the CME sessions (Table 1).

3.3. Willingness to receive LTBI treatment

The median (IQR) self-rated willingness score of the participants towards the acceptance of an effective LTBI preventive therapy regimen on a 10 point continuous rating scale with higher scores indicating greater acceptance was 6 (5.8) that increased to 8 (6) after the CME sessions (P = 0.02). The reasons attributed to non-acceptance of treatment for LTBI were concerns over side effects 19 (31.7%), emergence of drug resistance 11 (18.3%) and the likelihood of reinfection 4 (6.7%). Although, the participant's concern over contracting TB disease due to clinical exposure to microbiologically confirmed TB cases on a 10 point continuous rating scale indicated a higher median (IQR) score, 8 (5), it did not correlate significantly with their attitude towards personal acceptance of preventive therapy for treating LTBI (r = 0.215, p = 0.09).

3.4. Use of personal protective equipment

A total of 43 (71.7%) participants reported usually using surgical masks and 10 (16.7%) N-95 masks during clinical practice on encountering patients with symptoms suggestive of pulmonary TB. However, the frequency of the use of masks for

Table 1 – Awareness of LTBI epidemiology and management in participants.

Question	Correct response (pre-test) (n = 60) no. (%)	Correct response (post-test) (n = 47) no. (%)	P value
Global burden LTBI	10 (16.7)	19 (40.4)	0.002
Annual rate TB decline in India (current)	15 (25)	21 (44.7)	0.049
Annual rate TB decline in India for elimination	18 (30)	29 (61.7)	0.003
LTBI Rx in RNTCP	9 (15)	18 (38.3)	<0.01
Indian burden LTBI	20 (33.3)	32 (68.1)	<0.01
LTBI burden in HCW	37 (61.7)	39 (83)	0.004
LTBI Rx in low burden	14 (23.3)	17 (36.2)	0.12
Lifetime risk of TB	19 (31.7)	23 (48.9)	0.21
Risk LTBI on exposure	5 (8.3)	2 (4.3)	0.37
Risk active TB period	14 (23.3)	32 (68.1)	<0.01
Active TB risk groups	11 (18.3)	21 (44.7)	0.25
IGRA diagnosis	22 (36.7)	21 (44.7)	0.24
TST cut-off diagnosis	37 (61.7)	44 (93.6)	<0.01
IGRA sensitivity	9 (15)	14 (29.8)	0.002
C-TB LTBI detection	5 (8.3)	27 (57.4)	<0.01
INH Rifapentine	11 (18.3)	43 (91.5)	<0.01
LTBI Drug resistant Rx	14 (23.3)	22 (46.8)	0.007
INH Hepatotoxicity	53 (88.3)	46 (97.9)	0.62
Total knowledge score Mean (SD)	5.2 (2.2)	10.2 (2.2)	<0.01

Table 2 – Participant perspectives on expansion of LTBI management in India.

Question	Response (pre-test) (n = 60) no.(%)	Response (post-test) (n = 47) no.(%)
Agreement towards expansion of LTBI management under RNTCP for close contacts of pulmonary TB cases		
i. Yes without LTBI confirmation	11 (18.3)	6 (12.7)
ii. Yes but after LTBI confirmation	16 (26.7)	15 (31.9)
iii. Yes, but only in those with comorbidity	25 (41.7)	24 (51)
iv. Not sure/No definitive opinion	3 (5)	1 (2.1)
v. No, it will not be useful	5 (8.3)	1 (2.1)

personal protection was suboptimal with participants reporting their mask usage as being never 10 (16.7%), rarely 9 (15%), sometimes 25 (41.7%), often 10 (16.7%) and always 6 (10%).

3.5. *Perspectives on expansion of LTBI management in India*

On post-test, a majority (51%) of the participants supported a limited expansion of LTBI management in India by restricting preventive therapy to only those TB disease contacts having additional comorbidities (Table 2).

4. Discussion

We conducted a cross-sectional analysis on awareness and perspectives on expansion of latent TB management among medical doctors and intern trainees during a continuing medical education program in New Delhi, India. The present study shows that awareness of updated LTBI management guidelines in medical doctors is suboptimal. Treatment for LTBI was perceived to be associated with significant side effects and lack of sustained benefits by a majority of physicians.

Treatment for LTBI either through IPT or through newer regimens is not routinely offered in Indian healthcare settings, primarily due to concerns over its long-term efficacy in populations that experience repeated exposure to TB.[14] Our study further corroborates the evidence from previous studies that highlighted the phenomenon of treatment hesitancy among HCWs towards accepting treatment for LTBI. A study in the city of Pune in Western India by Kinikar et al (2019) reported that only two out of 60 medical/nursing trainees detected with prevalent and incident LTBI, initiated and completed IPT despite the offer for free treatment.[8] Another study in South Korea reported only 51.2% of HCWs adhered to their doctor's recommendation for LTBI treatment.[15]

Nevertheless, in our study, most physicians perceived themselves susceptible to TB disease during clinical exposure. Similarly, the study by Pardeshi et al (2017) among postgraduate resident doctors in Western India also reported a majority expressing concern over acquiring TB and drug resistant TB.[5] These findings indicate that physician perception of the usefulness of treatment for LTBI in preventing TB disease is limited, despite, their own apprehension over contracting TB disease at the workplace. However, in the present study, most physicians expressed readiness in adhering to WHO guidelines towards an expansive model of LTBI management among close contacts of TB cases. Maximum physicians supported LTBI treatment for comorbid patients but only after the confirmation of diagnosis using appropriate tests.

4.1. *Study implications*

Physician hesitation in accepting treatment for LTBI despite its proven efficacy has a sobering programmatic implication for the RNTCP since ensuring initiation, adherence and completion of preventive treatment for LTBI, both in currently eligible beneficiaries and on expansion, needs implementing primary care physicians to be convinced of its benefits. The generation of further medical evidence which quantifies the gain in health secured through treatment of LTBI especially in HCWs, and the amelioration of concerns over side-effects and reinfection are needed for improving the treatment acceptability.

Finally, on post-test, we found the physician attitude towards receiving treatment for LTBI was significantly more favorable, although the CME content had an exploratory design and was not a structured intervention for promoting acceptance for preventive therapy. However, the possibility of social-desirability bias influencing the physician post-test responses cannot be ruled out either.

4.2. *Study limitations*

The study had a small sample size with considerable heterogeneity in participant composition in terms of age and work experience. Moreover, the participants did not include other HCWs from alternative health systems, the private health sector and nursing personnel who are important stakeholders involved in the provision of care to TB patients.

Author contributions

Dr. Nandini Sharma contributed to design and data management.

Dr. Saurav Basu contributed to literature search, statistical analysis and manuscript preparation.

All the authors contributed towards the concepts, intellectual content, data analysis, drafting/editing of the article and approved the final manuscript being submitted.

Conflicts of interest

All authors have none to declare.

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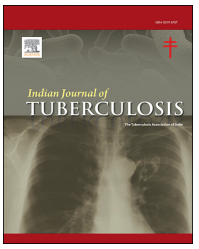

Original article

Impact of UDST: A step forward to end TB

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ABSTRACT

Background: India is determined to eliminate TB by 2025 despite being a high burden country. Revised National Tuberculosis Control Programme (RNTCP) is being strengthened with introduction of Universal Drug Susceptibility Testing (UDST) for Rifampicin to achieve the elimination status.

Methodology: We used a before–after comparison of baseline and intervention periods (12 months each) and analyzed data viz CBNAAT performed and case detection for both drug sensitive and drug resistant TB cases.

Results: After implementation of Universal DST, CBNAAT performed raised from 1252 to 3137 (increased by 2.5 times); Rif sensitive cases detected raised from 458 to 1241 (increased by 2.7 times) and Rif resistant cases detected raised from 54 to 82 (increased by 1.5 times) during baseline period (2017) and intervention period (2018).

Conclusion: We conclude that introduction of UDST for Rifampicin in RNTCP has given a significant impact with increased case detection in our study.

1. Introduction

The End TB strategy highlights integrated patient-centred care and prevention as its first pillar. 'Rapid molecular diagnostics' introduced in 2009 and scaled up in 2012 has ensured that Line Probe Assay and Cartridge Based Nucleic Acid Amplification Test (CBNAAT) are available throughout the country. The program has currently scaled up its policy of Universal Drug Susceptibility Testing (UDST) whereby all cases diagnosed with TB will receive a minimum of Rifampicin resistance testing, using high sensitivity tools like the CBNAAT.[1]

The recently launched National Strategic Plan (NSP) for 2017-25 has proposed ambitious plans towards elimination of TB in India through a four pronged approach - Detect, Treat, Prevent and Build.[2]

Detect - For detecting all drug-sensitive (DS-TB) and drug-resistant TB (DR-TB), the steps proposed are scaling up of highly sensitive diagnostics and algorithms, universal testing of drug-resistant TB and systematic screening of high-risk population. All this is possible through scale-up of private provider engagement. Launch of universal DST (Drug Sensitivity Testing) for all TB patients will increase the detection of DR-TB.

In Jhalawar, since January 2018, all newly diagnosed TB cases are being subjected to CBNAAT for confirmation of diagnosis and identifying sensitivity to Rifampicin. This study

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has been conducted to see the impact of UDST in detection of DS and drug resistant (DR) TB cases.

2. Material and methods

This study was conducted at Department of Respiratory Medicine, Medical College, Jhalawar in collaboration with TB Clinic- Jhalawar for a period from January 2017 to December 2018 to assess the impact of introducing Universal DST since January 2018 by comparing the data of case detection for both years.

3. Results

Table 1 and Fig. 1 depict that after implementation of Universal DST, CBNAAT performed and also detection of Rif sensitive as well as Rif resistant cases has got increased significantly. In 2017 when UDST was not implemented 1252 CBNAAT were performed which increased to 3137 (increased by 2.5 times) after starting UDST from January 2018. In 2017 we could find 458 microbiologically confirmed, Rif sensitive cases, which rose to 1241 (increased by 2.7 times) in 2018. In 2017, 54 Rif resistant cases were registered which lead to 82 cases (increased by 1.5 times) in 2018 after getting samples for UDST.

4. Discussion

As per the diagnostic algorithm of Revised National TB Control Programme: Technical and Operational Guidelines for Tuberculosis Control in India, CBNAAT was advised for smear positive and presumptive MDR TB, smear negative and chest X-ray suggestive of TB, PLHIV, pediatric TB and extrapulmonary TB cases.[4]

To achieve universal access to early accurate diagnosis of TB and enhancing case finding efficiency, identification of presumptive TB cases at the first point of care and linking them to the best available diagnostic tests is of paramount importance. This is reflected by introduction of universal DST, rolled out in a phased manner starting in 2017 by National strategic plan for tuberculosis elimination 2017–2025.[3]

In this study, we established the added value of expanding the diagnostic algorithm using Universal DST for all cases diagnosed with TB received a minimum of Rifampicin resistance testing, using high sensitivity tools like the CBNAAT. Specifically, we quantified the additional diagnostic yield in performing 2.5 times more CBNAAT testing and diagnosing 2.7 times more Rifampicin sensitive cases and 1.5 times more Rifampicin resistant cases from previous year.

Thus in this study we quantified the effect of implementation of Universal DST on more detection of DS and drug resistant (DR) TB cases in a before–after design. Introduction

Table 1 – A comparative analysis of CBNAAT performed and case detection before (2017) and after (2018) UDST.

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Total
CBNAAT performed (2017)	33	46	73	60	102	129	123	142	164	147	133	100	1252
CBNAAT performed (2018)	179	236	217	271	336	234	270	325	238	306	264	261	3137
MTB detected and Rif sensitive (2017)	20	17	31	29	43	57	49	51	48	43	38	32	458
MTB detected and Rif sensitive (2018)	49	76	80	109	135	122	114	135	89	125	98	109	1241
MTB detected and Rif resistant (2017)	1	2	7	7	5	4	3	4	4	10	3	4	54
MTB detected and Rif resistant (2018)	6	10	7	8	9	4	8	9	7	6	6	2	82

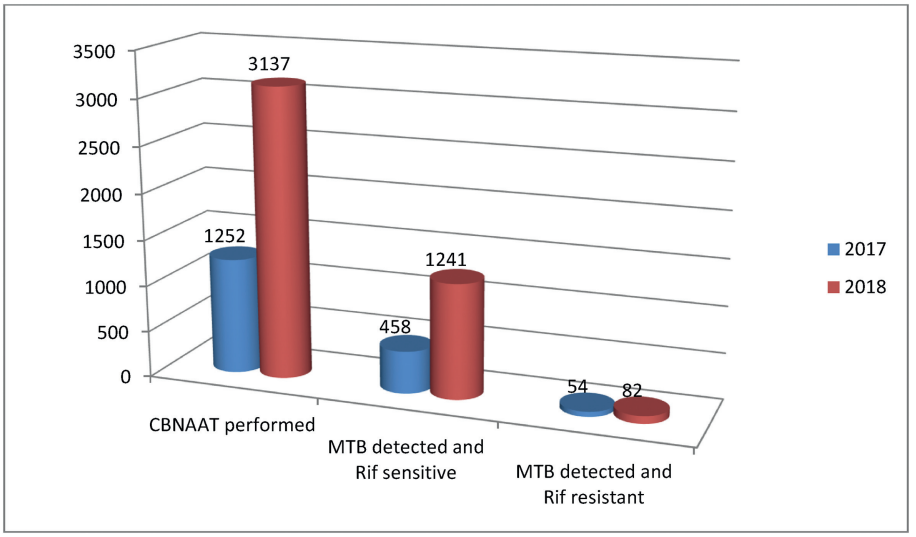

Fig. 1 – A comparative analysis of CBNAAT performed and case detection before (2017) and after (2018) UDST(Graph).

of Universal drug susceptibility testing for Rifampicin clearly was a decisive factor.

5. Conclusion

We conclude that universal DST has given a significant impact with increased case detection in our study. Early case detection is vital to interrupt the transmission of TB disease and strategy will largely determine the response to appropriate treatment.

Conflicts of interest

The authors have none to declare.

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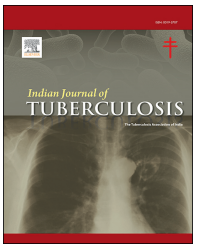

Original article

Ocular adverse events in drug sensitive TB patients on daily fixed dose combination anti-TB drugs: A record review study from Kerala, India

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ABSTRACT

Background: Government of India's Revised National TB Control Programme (RNTCP) has begun implementing daily fixed dose combination (FDC) anti-TB treatment regimen for drug sensitive TB patients in which ethambutol is given for six months. Prolonged ethambutol use is known to cause ocular adverse drug events (ADE).

Objectives: To assess the magnitude of ocular ADEs in adult drug sensitive TB patients initiated on daily FDCs and to describe the demographic and clinical profile of patients with ocular ADEs.

Methods: We conducted a retrospective cohort study involving review of RNTCP records of all adult (age >14 years) drug sensitive TB patients initiated on daily FDCs between1st January 2018 and 31st July 2018 in Thiruvananthapuram district, Kerala State, India.

Results: 714 patients were initiated on daily FDCs during the study period. It was unknown whether all patients had undergone assessment for ocular ADEs. However, of these 714 patients, 8 patients (1.1%) were documented to have had ocular ADEs. Seven of these 8 patients had received ethambutol more than 15 mg/kg body weight and had developed ocular symptoms (decreased/blurring of vision) 3 months after TB treatment initiation. Ethambutol was stopped in all these 8 patients. In 5 patients it was recorded that ocular ADEs had resolved following stoppage of ethambutol and in the remaining it was unknown.

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Conclusion: The study confirms the occurrence of ocular ADEs among drug sensitive TB patients on daily FDCs and recommends strengthening of systems for assessing, documenting and managing ocular ADE.

1. Introduction

India is one of the high tuberculosis (TB) burden countries in the world with an estimated annual incidence of 2.79 million patients accounting for about a quarter of the world's TB cases.[1] In order to eliminate TB by 2025, India's Revised National TB Control Programme (RNTCP) had developed a national strategic plan (2017–2025).[2] In accordance with this plan, newer diagnostic services, drugs, treatment schedules, treatment adherence monitoring and surveillance mechanisms have been introduced. Introduction of daily anti-TB treatment regimens containing fixed dose combination (FDC) of first line anti-TB drugs by replacing intermittent therapy has been one of the key recent changes in the management of drug sensitive TB.[3]

Though the effectiveness and positive therapeutic effects of FDCs of first line anti-TB drugs in the treatment of TB has already been accepted, this approach reportedly leads to higher instances of adverse drug events (ADEs).[3] The overall prevalence of ADEs with first line anti tubercular drugs range from 8% to 85%,[4] which include hepatotoxicity, gastrointestinal (GI) disorders, allergic reactions, arthralgia, neurological disorders, ocular manifestations etc.[4–7] These ADEs can lead to treatment non-adherence, increase patient suffering and substantial additional expenses due to added outpatient visits, tests, and hospitalizations.[6,7] These ADEs are of varying severity depending on drugs, dosages, duration of intake and also comorbid conditions.[5–7]

Ocular ADEs can occur with first line anti-TB treatment which manifests in the form of blurred vision, decreased visual acuity and loss of red green color vision and has been reported in 0.1%–6% of the patients.[8–10] Most of these ocular ADEs are due to ethambutol.[11] Even though exact mechanism of ocular neurotoxic effect of ethambutol is not identified, studies on rodents and monkeys have demonstrated functional and morphological damages by ethambutol predominantly on the retinal ganglion neurons.[12] The hypotheses for ethambutol induced ocular toxicity include the zinc chelating effect of EMB and its metabolite on various mitochondrial metal-containing enzymes and the excitotoxic pathway.[13,14] The ethambutol induced disruption of oxidative phosphorylation and mitochondrial function by interfering with the iron and copper containing complexes results in generation of a reactive oxygen species leading to tissue injury and cellular apoptosis mainly in retinal ganglion neurons.[14]

Isoniazid can also cause bilateral optic neuritis especially when used in combination with ethambutol. It is also documented that persistence of ocular ADEs even after 3 months of discontinuation of ethambutol is due to the effect of isoniazid.[15] Increased age, hypertension, poor renal function, diabetes, HIV, tobacco and alcohol intake have also been identified as risk factors for ocular ADE.[16–19]

In India, there have not been any studies on the occurrence of ocular ADEs under routine programmatic conditions after the implementation of the daily FDC regimen in which ethambutol is being used for a minimum duration of 6 months. The current RNTCP guidelines recommend that patients on anti-TB treatment must be periodically evaluated for all ADEs including ocular ADEs. However, the extent of implementation of these guidelines is unknown.

Considering the paucity of data on ocular ADE, we undertook an operational research study in Thiruvananthapuram district of Kerala, a South Indian State. The aim of this study was to assess the magnitude of ocular ADEs among adult drug sensitive TB patients on daily FDC anti-TB regimen documented in the RNTCP's recording and reporting system and to describe the demographic and clinical profile of the TB patients with ocular ADEs.

2. Methods

2.1. Study design

It was a retrospective cohort study involving review of secondary data from RNTCP records.

2.2. Setting

Kerala is a state, in the south western part of India with an area of 38,863 sq. km. and a population of 33.38 million. The state has the highest overall life expectancy at birth (74.9 years), lowest rates of maternal mortality (66/100,000 live births) and childhood malnutrition (23%). Kerala is one of the low TB burden states in the country. The total TB notification rate in this state was 67 per 100,000 populations, far below the average national notification rate of 138 per 100,000 population.[20] The study was conducted in Thiruvananthapuram District (population ~3.4 million), one of the fourteen districts in the state of Kerala.

2.3. RNTCP in Thiruvananthapuram

There is a District TB Centre (DTC), seven Tuberculosis units (TUs), 51 Designated Microscopy Centers (DMC), 110 Peripheral Health Institutions (PHIs), two Cartridge Based Nucleic Acid Amplification Test (CBNAAT) facility sites, and one Drug Resistant Tuberculosis (DR-TB)Centre at Government Medical college, Thiruvananthapuram.

The district started implementing daily FDC first line anti-TB regimen since August 2017. All drugs are provided free of cost to all the patients enrolled for treatment under RNTCP. About 150 TB drug sensitive TB patients (aged ≥14 years) are initiated on first line FDCs in the district per month. Resistance to rifampicin is tested with CBNAAT for all smear positive cases and those found to be rifampicin resistance are treated with a drug resistant TB treatment regimen with second-line drugs. The first line FDC anti-TB treatment regimen contains 2 months of intensive phase containing Isoniazid, Rifampicin, Ethambutol and Pyrazinamide and 4 months of continuation phase containing Isoniazid, Rifampicin and Ethambutol. The drugs are self-administered and the dose is dependent on the patient's body weight as given in Table 1. The patients' treatment details are captured through the TB treatment cards and Nikshay (web-based TB patient recording and reporting system).[20] The TB treatment card has provisions for entering important information of the patient like name, age, sex, weight, address, history of previous treatment, baseline investigations (sputum smear, CBNAAT, X-ray), type of disease, co-morbidities, treatment regimen, duration of treatment, adverse events and treatment outcome. As per the RNTCP guidelines, all TB patients are expected to undergo ophthalmic examination by an ophthalmologist if they report ocular symptoms anytime during the TB treatment. If the ophthalmologist determines that the ocular symptoms are due to anti-TB treatment, then ethambutol is discontinued and this is documented in the RNTCP records (treatment cards).

2.4. Study population, study site, and study period

Records of all adult (age >14 years) drug sensitive TB patients initiated on daily FDC anti-TB regimen between1st January 2018 and 31st July 2018 in Thiruvananthapuram district, Kerala were included in the study. We reviewed the TB treatment cards of these patients in the months of December 2018 and January 2019 to assess if they had ocular ADE anytime during the TB treatment.

2.5. Data variables, sources of data and data collection

A list of all adult drug sensitive TB patients initiated on treatment from 1st January 2018 to 31st July 2018 was prepared from Nikshay. The treatment cards of all these patients were reviewed by the Principal Investigator (MSM) after the completion of treatment. Data variables collected from each TB treatment card were: Nikshay ID, age, gender, weight, type of patient (new, recurrent, treatment after failure, treatment after lost to follow-up, transfer-in and others), case definition (microbiologically confirmed or clinically diagnosed), site of disease (pulmonary/extra-pulmonary), diabetes status, HIV status, substance use (current tobacco, current alcohol use) and TB treatment regimen. In addition, we also assessed if there was a documentation of ocular ADE, symptoms, date of adverse event, action taken, date of resolution of adverse event, outcome of TB treatment.

Table 1 – Drug Dosage of daily fixed dose combination of first line anti-TB drugs used for adult drug sensitive tuberculosis patients under the Revised National TB Control programme in India.

Weight category	Number of tablets (FDCs)	
	Intensive Phase	Continuation phase
	HRZE[a] (75,150,400,275) mg	HRE[a] (75,150,275) mg
25–39 kg	2	2
40–54 kg	3	3
55–69 kg	4	4
≥70 kg	5	5

[a] H- isoniazid, R- Rifampicin, Z- Pyrazinamide, E-Ethambutol.

2.6. Analysis and statistics

Data were collected into a structured format created in Microsoft Excel, imported into the statistical software EpiData Analysis (Version: 2.2.2.183, EpiData Association, Odense, Denmark). We have summarized the demographic and clinical variables of the all patients enrolled for TB treatment using numbers and proportions. As a small number of patients who developed ODE, we have presented their individual case profile.

2.7. Ethics

Ethics approval was obtained from the Ethics Advisory Group of the International Union against Tuberculosis and Lung Disease, Paris, France and administrative approval to conduct this study was obtained from the State TB Office, Kerala. As the study involved review of existing patient records, we were given waiver from obtaining informed consent from patients.

3. Results

A total of 714 adult TB patients were initiated on daily first line FDC Anti-TB treatment regimen from 1st January to 31st July 2018. The demographic and clinical characteristics of these patients are given in Table 2. About 72% were males, mean age was 48 years (standard deviation of 17 years), 91% were new TB patients, 72% had pulmonary TB disease, 62% were microbiologically confirmed, 0.3% was HIV seropositive and 22% had diabetes mellitus.

Seventy seven patients had adverse drug events recorded. These were ocular in 8 (1.1%) patients, gastrointestinal in 29 (4.1%) patients, dermatological in 26 (3.6%) patients, joint pain in 12 (1.7%) patients, hearing impairment in 1 (0.1%) and hepatic impairments in 1 (0.1%) patient.

Ethambutol was discontinued for all 8 patients with ocular ADE. The demographic and clinical profile of these eight patients is given in Table 3. These eight patients were above the age of 40 years, with equal number of males and females. All patients had either decreased or blurred vision and in seven of these patients the symptoms were reported after 3 months of treatment initiation. Seven out of these eight patients had received ethambutol more than 15 mg/kg body weight during treatment prior to ocular ADE. At the time of record review, all patients had completed their TB treatment with a successful

Table 2 – Demographic and clinical characteristics of adult drug sensitive TB patients initiated on daily regime* in Thiruvananthapuram district, Kerala, India (January–July 2018).

Characteristics		Number	(%)
Total		714	(100)
Age (in years)	Mean (SD)	48 (17)	
Gender			
	Male	517	(72)
	Female	197	(28)
Type of patient			
	New	653	(91)
	Recurrent	24	(4)
	Treatment after failure	7	(1)
	Treatment after lost to follow up	8	(1)
	Others	6	(1)
	Not Recorded	16	(2)
Case definition			
	Microbiologically confirmed	442	(62)
	Clinically diagnosed	268	(37)
	Not Recorded	4	(1)
Site of disease			
	Pulmonary	515	(72)
	Extra pulmonary	181	(25)
	Not Recorded	18	(3)
Co-morbidities			
	Hypertension	28	(4)
	Diabetes	157	(22)
	HIV	2	(0.3)
	Others^	19	(3)
Substance Abuse			
	Current Tobacco use (Smoked forms)	95	(13)
	Current Tobacco use (Smokeless forms)	5	(0.7)
	Current Alcohol use	96	(13)
	Not Recorded	312	(44)

% column percent *daily regime: regime containing fixed dose combinations of antitubercular drugs taking on daily basis. ^Other co-morbidities include CAD, Cancer, CVA (stroke).

outcome (cured/treatment completed). There were three diabetics, one hypertensive, three current tobacco users and two alcohol users among the eight patients with ocular ADEs and whether these factors had any influence on ocular events is not clear from the records. Resolution of ocular ADE was documented in records of five patients and in the remaining it was unknown.

4. Discussion

This is the first study to look into the occurrence of ocular ADEs under routine programmatic conditions in India after the implementation of the daily FDC anti-TB treatment regimen and it confirms the occurrence of ocular ADEs.

The major strength of the study was that it covered a large number of TB patients and was conducted under routine programmatic conditions. As our study was retrospective in nature and was done after the TB treatment outcomes were declared, it is unlikely that our study procedures would have influenced the recording and reporting of ocular ADEs. Therefore, the study findings reflect what was happening at the field level—which was one of the primary purposes of choosing this retrospective record review methodology in our operational research study. The major limitation of these study findings may not be generalizable to other districts in the state nor in the country as it was done in one district of Kerala and is dependent on the probability of medical officers and other health staff documenting the ADEs in the RNTCP records in proper manner.

Despite this limitation, a few important observations were made which we feel have implications on policies and practices—both national and international.

First, the profile of patients enrolled for treatment (Table 2) indicates presence of several risk factors for the occurrence of ocular ADE. Notable among these were higher mean age, tobacco and alcohol consumption and diabetes mellitus. Therefore, it is essential for the RNTCP to monitor the occurrence of ocular ADE in these patients that are getting enrolled for treatment.

Second, we have observed that there was no documentation in the treatment cards or in the NIKSHAY portal about whether all TB patients have systematically undergone pre-treatment assessment or periodic assessment for ocular ADEs during the course of TB treatment. The ocular ADEs vary from mild symptoms to extreme cases with loss of vision. Without periodic systematic evaluation of all cases, there is a possibility of late diagnosis or missed diagnosis of ocular ADEs. Furthermore, as per our study methodology we reviewed only RNTCP records (TB treatment cards and patient data in NIKSHAY). It is possible that due to deficiencies in recording information, several instances of mild ocular ADE could have been missed from being documented. Therefore, the magnitude of ocular ADEs reported in our study is likely to be a gross underestimate and most likely indicates only the serious forms that resulted in discontinuation of ethambutol.

Third, an analysis of the profile of these eight cases indicated that seven were receiving ethambutol >15 mg/kg body weight. Previous studies have highlighted that ethambutol >15 mg/kg body weight is associated with the occurrence of ocular ADE.[21–23] The drug dosages prescribed by RNTCP is based on weight bands in which people within a certain body weight range receive standard fixed doses of all anti-TB drugs (as described in Table 1). This may result in higher dosages for certain small sub-group of patients whose body weights fall in the borderline. We, therefore, recommend intense monitoring of ocular ADEs in such patients.

Fourth, we feel that deficiencies in recording of ocular ADEs is also partly due to the current RNTCP technical and operational guidelines which recommend ocular evaluation by a specialist only 'if indicated' for drug sensitive cases without clear guidance on what this means or how this needs to be implemented.[3] We therefore recommend that RNTCP should revisit its guidelines and recommend periodic/regular assessment of all cases for ocular ADEs especially if they have risk factors. Identifying the optimal method for implementing the periodic ocular ADE assessment (frequency, the nature of these assessments, tools etc.) under routine programmatic

Table 3 – Characteristics of the patients with reported ocular adverse events among adult drug sensitive TB patients on daily regime in Thiruvananthapuram district, Kerala, India (January–July 2018).

Age	Gender	Patient type	Site of Disease	Case Definition	Co morbidities	Substance Abuse	Ethambutol Dose (mg)	Duration between treatment initiation and occurrence of ocular ADE (in days)	Other adverse events	Treatment outcomes
50	M	New	Pulmonary	Microbiologically confirmed	No	No	1375 (18 mg/kg)	134	Dermatological	Cured
51	F	New	Extra pulmonary	Microbiologically confirmed	HTN	No	1375 (16 mg/kg)	34	Gastrointestinal & Joint pain	Treatment Completed
66	F	Recurrent	Extra pulmonary	Clinically diagnosed	No	No	825 (20 mg/kg)	87	Nil	Treatment Completed
63	F	New	Pulmonary	Microbiologically diagnosed	DM	No	1100 (19 mg/kg)	153	Gastrointestinal	Cured
64	M	Recurrent	Pulmonary	Microbiologically diagnosed	DM	Tobacco	825 (20 mg/kg)	152	No	Cured
40	M	New	Pulmonary	Microbiologically confirmed	No	Tobacco & Alcohol	550 (14 mg/kg)	157	No	Cured
60	M	New	Pulmonary	Microbiologically confirmed	DM	Tobacco & Alcohol	1100 (19 mg/kg)	121	No	Cured
62	F	New	Extra pulmonary	Clinically diagnosed	No	No	825 (20 mg/kg)	94	No	Treatment Completed

M-male, F- Female, HTN- Hypertension, DM- Diabetes Mellitus.

conditions is a subject matter for the future operational research studies. Several simple tests/tools like symptom screening, Snellen's chart for checking visual acuity,[24] pseudo isochromatic tests for color blindness[25] are available which can be used at the field level by peripheral health workers to assess ocular ADEs. Apart from this, RNTCP in Kerala has designed a checklist for identifying all possible minor and major ADEs. This checklist has been rolled out in the field towards to end of 2018 and whether this is suitable or not for identifying ocular ADEs may be assessed in future research.

Lastly, due to limitation of the data recorded, we were unable to assess the challenges in the management of the ocular ADEs. In 5 out of 8 patients it was documented that the ocular symptoms had subsided or resolved and in all 8 patients, ethambutol was discontinued from TB treatment. The non-availability of the status of Ocular ADE in 3 patients is still a limitation as it may be due to the non-resolution of the adverse event rather than lacunae in recording and reporting system. The recovery of non-resolving ocular ADEs may take several months[26] and for capturing these delayed outcomes proper prolonged follow up monitoring systems has to be established. We also assessed whether the discontinuation of ethambutol had any adverse effect on the TB treatment outcome. But fortunately, none of the eight patients had any adverse TB treatment outcome till the time of assessment. Moreover, for a complete understanding of incidence, predisposing factors and management of ocular ADEs, more prospective cohort studies have to be undertaken.

5. Conclusions

Our study confirms the occurrence of ocular ADEs among drug sensitive TB patients on daily FDC anti-TB regimen. The systems for assessing, documenting and managing ocular ADE appears to be ill-defined and needs to be strengthened in order to improve the quality of TB treatment services under RNTCP.

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Conflicts of interest

The authors have none to declare.

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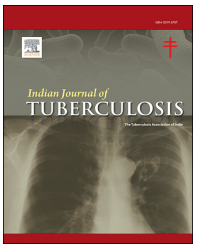

Original article

Early treatment outcome of bedaquiline plus optimised background regimen in drug resistant tuberculosis patients

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ABSTRACT

Aims: Bedaquiline (BDQ) has been recently approved for drug resistant tuberculosis with active drug safety monitoring under programmatic condition. The present study was conducted to evaluate safety, tolerability and efficacy of bedaquiline plus optimised background regimen.

Methods: A prospective study was conducted on cohort of pre-extensively drug resistant (XDR) and XDR pulmonary TB patients. Eligible patients were closely monitored for cardiac safety, adverse events (AEs), clinical and microbiological improvement during BDQ (6 months) and post BDQ phase for twelve months.

Results: Of 127 patients enrolled, a significant increase in mean QTc interval was observed on 13th day and 3rd week as compared to baseline ($p < 0.0001$). Mean maximum increase of QTc was 37.92ms (95% CI, 14.1–61.74ms). Concomitant anti-TB medications, age, gender, low body mass index (BMI) had significant effect on QTc prolongation ($p < 0.0001$, $p < 0.05$). However, none of the patient required discontinuation of BDQ. Majority of AEs (86.3%) were non-serious and not preventable 108 (87.1%). The median time for sputum-culture conversion was 40.89 ± 3.5 days (95% CI, 34–48 days) and the treatment outcome was successful in 102 (80.3%) patients with negative sputum culture conversion.

Conclusions: Bedaquiline containing regimen achieved favourable outcome. Although, bedaquiline along with concomitant anti-TB medications has the potential to prolong QTc interval, the benefit certainly outweighs the risk. This calls for a through pre-treatment cardiovascular and biochemical evaluation as a preventive measure and appropriate selection of patients for safe use of BDQ and successful outcome.

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Statement 1: What is already known about this subject?

- In India, a special approval for '*compassionate use*' of bedaquiline under strict active drug safety monitoring (Cohort event monitoring) was given to generate data for its continued use and decision making for regulators for subsequent wider access in the country.

Statement 2: What this study adds

- The high and rapid sputum culture conversion rate and absence of unexpected serious adverse events indicates that bedaquiline containing regimen is well tolerated and strengthens DR-TB treatment.
- Bedaquiline significantly prolongs QTc interval. Pre-treatment biochemical and cardiac assessment followed by close monitoring will be essential for safe use of bedaquiline. The benefit certainly outweighs risk.

1. Introduction

India continues to have highest number of tuberculosis cases in the world.[1] The National Anti-TB Drug Resistance Survey for 2014–16 reported that resistance to any drug was 28.02%, with 6.19% MDR-TB patients and among them 1.3% were XDR-TB.[2]

Unfortunately, until mid-2016, the treatment landscape for drug resistant tuberculosis (DR-TB) had remained unchanged resulting into low successful treatment outcome with nearly 50% mortality.[3,4] In view of DR-TB, a disease of special relevance to Indian health scenario with lack of effective therapy, a new drug bedaquiline (BDQ) was given special approval for '*compassionate use*' under strict active drug safety monitoring (Cohort event monitoring) by Apex Committee under Supreme Court of India in 2016.

Being a new drug with limited clinical experience and exemption of domestic clinical trial, active drug safety monitoring was most vital to generate data for its continued use and decision making for regulators for subsequent wider access in the country. Thus, the present study was undertaken to evaluate the safety, tolerability and efficacy of BDQ in combination with an Optimized Background Regimen (OBR) as per drug susceptibility test (DST) in DR-TB patients in programmatic, non-clinical trial condition.

2. Methods

2.1. Study design

It was an observational, continuous, prospective, single centre study in cohort of DR-TB patients conducted at Nodal DR-TB center and Department of Pharmacology, B. J. Medical College, Ahmedabad, a tertiary care teaching hospital for 28 months (July 2016 to October 2018).

2.2. Inclusion and exclusion criteria

Patients having pre-XDR and XDR pulmonary TB, more than 18 years of age, normal electrocardiogram (ECG), and QTc interval below 450ms were enrolled. Patients having uncontrolled cardiac arrhythmia and/or co-morbid cardiac conditions that required medication or QTc interval (>450ms) at screening, pregnancy, women using non-hormonal based birth control methods, were excluded.

2.3. Pre-treatment assessment

Subsequent to ethics committee approval and written informed consent, all eligible patients were evaluated for ECG, chest x-ray, haematological and biochemical investigations, urine gravindex, sputum culture and DST (CBNAAT and Line Probe Assay).

2.4. Study end points

2.4.1. Primary

i) Specific Adverse events (AEs):QT prolongation, its severity and outcome
ii) General AEs

2.4.2. Secondary

i) Microbiological improvement: Sputum culture conversion time and rate by liquid culture. Patient was considered 'culture converted' when two consecutive cultures, taken at least 30 days apart were negative.
ii) Clinical improvement: Increase in body weight

2.5. Designing of drug regimen

All eligible patients were prescribed bedaquiline along with at least four second line effective anti-TB medications as OBR according to WHO treatment guidelines for DR-TB (2016) and DST results. The choice of second line anti-TB drugs in the descending order was kanamycin/capreomycin (second-line injectables); levofloxacin/moxifloxacin (fluoroquinolones); ethionamide/cycloserine/PAS; linezolid/clofazimine/high-dose isoniazid/clarithromycin and pyrazinamide, if sensitive.

2.6. Treatment protocol and follow up

Bedaquiline was administered as 400 mg daily for initial fourteen days followed by 200mg thrice a week for next 22 weeks (total six months) along with OBR for 18 months. All patients receiving bedaquiline were hospitalised for initial fourteen days and monitored intensively. Daily ECG and QTc interval were measured in lying down position preferably in the morning using standardised BPL CARDIART 6208 VIEW machine having 12 leads. The QTc interval was corrected with

Bazett formula: Corrected QTc interval = QT × (1000 ÷ RR interval in milliseconds)[1/2]

2.7. Cohort event monitoring

Each patient was monitored for AEs, clinical and microbiological improvement during BDQ phase and post BDQ phase (Fig. 1).

2.8. Initial fourteen days

Each patient was hospitalized and closely monitored for AE, daily ECG and QTc interval. Sputum culture and haematological tests were repeated at the end of first and second week.

2.9. Follow up

2.9.1. From 2nd week to end of 6 months

ECG and QTc interval, sputum culture, CBC/platelets, liver and renal function tests, serum electrolytes and urine gravindex was repeated monthly till the end of six months. Chest X-ray and thyroid function tests was repeated at the end of six months.

2.9.2. From 7th month to end of 18 months

Haematological investigations and sputum culture analysis was done at 7th, 9th, 12th, 15th, 18th months of treatment. While chest X-ray was repeated at 12th and 18th months of treatment. All spontaneous AEs reported by patient or treatment supervisor were recorded and followed up till recovery.

3. Result

A total of 127 DR-TB patients were enrolled. The characteristic of the patients is shown in Table 1. Majority of the patients were young (<30yrs.), had low body mass index (BMI) (<18.5kg/m2) and were previously treated with anti TB drugs.

Table 1 – Baseline general characteristics of the DR-TB patients in the study (n = 127).

Parameter	DR-TB patients on DST guided regimen
Mean age ± SD (Years)	30.75 ± 0.9 years
Gender:	
Men (%)	69 (54.33)
Women (%)	58 (45.67)
Mean Body weight ± SD (kg)	43.14 ± 8.17 kg
Mean height ± SD (cm)	159.1 ± 8.3 cm
Body mass index (BMI) kg/m2	
<18.5 (%)	94 (74.02)
18.6–24.9 (%)	32 (25.19)
>25 (%)	1 (0.79)
Personal habits	
Smoking (%)	27 (21.26)
Tobacco chewing (%)	12 (9.45)
Alcohol Consumption (%)	04 (3.15)
Smoking (%) + Tobacco (%)	04 (3.15)
Tobacco (%) + Alcohol (%)	01 (0.79)
Smoking (%) + Alcohol (%)	03 (2.36)
No habits	76 (59.84)
Family history of TB (%)	20 (15.7%)
Previous TB treatment	
Cat I	109 (85.8%)
Cat II	48 (37.8%)
Cat IV	110 (86.6%)

3.1. Pattern of drug resistance and OBR

All patients were resistant to isoniazid and rifampicin (100%) followed by levofloxacin (116, 91.3%), moxifloxacin (92, 72.4%), pyrazinamide (64, 50.4%), kanamycin (39, 30.7%), and capreomycin (32, 25.2%). Of 127 patients, 40 had XDR and 87 pre-XDR TB.

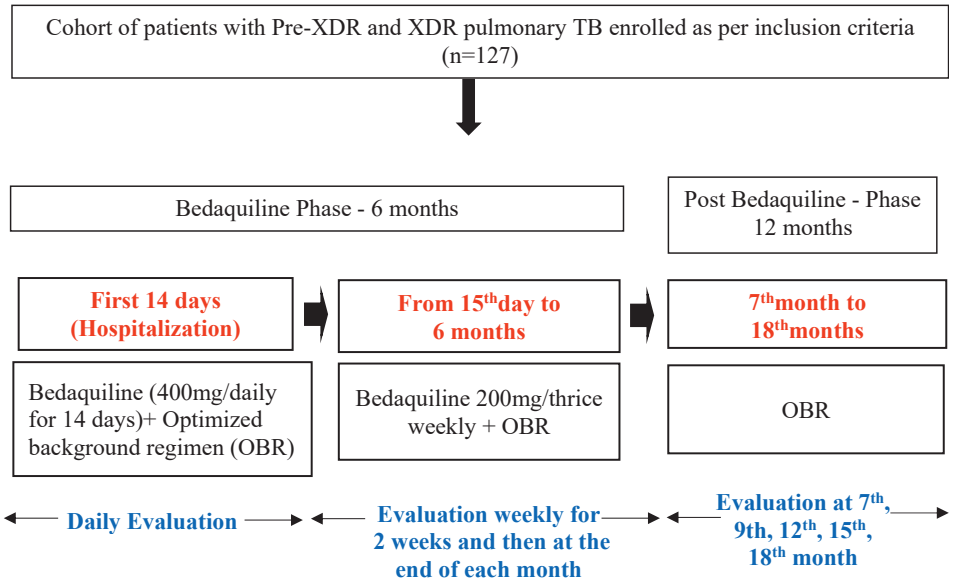

Fig. 1 – Study design.

3.2. Treatment safety profile

A total 124 (97.6%) AEs were observed. The most common was gastrointestinal (24, 19.4%) followed by skin and appendages (21, 16.9%) and body as a whole (17, 13.7%). Vomiting (11, 8.9%) was the most common clinical presentation followed by anorexia, diarrhoea, nausea and abdominal pain while skin discolouration (12, 9.7%) was the most common in skin and appendages disorders followed by rashes, acneiform facial eruptions (Table 2).

There were fourteen deaths (11%), one had long standing diabetes mellitus with myocardial infarction while all others had extensive tuberculosis disease. All these were non-responder and had persistently positive sputum culture at the time of death.

3.2.1. Cardiovascular AEs and QTc prolongation

A significant increase in mean QTc interval was observed on 13th day and 3rd week in patients treated with BDQ plus OBR as compared to baseline ($p < 0.0001$) (Fig. 2). The mean QTc interval remained persistently high for four months and gradually returned to almost baseline by end of the study. However, one patient showed QTc prolongation (444.44 ms, baseline 270 ms) with ventricular premature contraction (VPC) (3:1) on 4th day of treatment. Bedaquiline was stopped temporarily for a day. Biochemical examination revealed hypocalcaemia and VPCs were resolved with calcium replacement. Bedaquiline was reintroduced and no further cardiac rhythm abnormality was detected.

A detail analysis of QTc interval showed that the mean maximum increase in QTc was 37.92 ms (95% CI, 14.1–61.74 ms). Majority of patients (113, 88.9%), the increase in QTc was less than 50 ms. While it was more than 50ms (51–60 ms) in 11 (8.9%) patients and more than 60ms in 13 (10.24%). BDQ was not discontinued permanently in any patient.

3.3. Effect of different variables on QTc interval

An attempt has been made to analyse the effect of variables like concomitant anti TB drugs, age, gender and BMI on QTc interval.

3.3.1. Concomitant drugs with potential effect on QT interval

In addition to BDQ, moxifloxacin (Mfx), clofazimine (Cfz) and linezolid (Lzd) have potential to prolong QTc interval.[5,6] Out of 127 patients, four (3.15%) received only bedaquiline; while 48 (37.8%) two drugs (Bdq + Cfz/Bdq + Mfx/Bdq + Lzd), and 65 (51.2%) three drugs (Bdq + Lzd + Cfz/Bdq + Lzd + Mfx), whereas ten (7.9%) patients received all four drugs (Bdq + Lzd + Cfz + Mfx).

It was observed that QTc interval was significantly prolonged in patients treated with concomitant drugs, albeit the extent and time period was not consistent (Table 3). A significant increase in mean QTc interval was observed in bedaquiline treated patients (23.75 ms) at 3rd month ($p < 0.05$). Similarly, patients treated with two drugs showed significant increase of 10.81 ms ($p < 0.0001$) and 8.188 ms ($p < 0.05$) at 14th day and 3rd week respectively. While patients treated with three anti-TB drugs showed significant increase in QTc interval of 13.69 ms ($p < 0.0001$), 16.18 ms ($p < 0.0001$), 18.44 ms ($p < 0.0001$) and 9.136 ms ($p < 0.05$) 14th day, 3rd week, 3rd month and 6th month respectively. However, patients treated with all four anti-TB drugs showed increase in QTc interval with maximum increase in mean QTc interval (31 ms) at 3rd week (small sample limited statistical analysis) (Table 3).

3.3.2. Age and gender

A significant increase in QTc interval (21.9ms) was observed in 46–70 years age group ($p < 0.05$) and more in women as compared to men (18.7ms, $p < 0.05$).

Table 2 – Clinical presentation of adverse events DR-TB patients treated with bedaquiline plus optimized background regimen (n = 127).

Events	Number	Suspected Drug
Vomiting and Abdominal discomfort/Nausea/Diarrhoea/Anorexia/fever	33	Ethionamide/Linezolid/Bedaquiline/PAS
Skin & Dental discolouration/Redness of skin/Rashes/Acneiform eruption	18	Clofazimine/Pyrazinamide/Ethionamide
Chest pain with QTc prolongation	11	Bedaquiline/Clofazimine/Linezolid/Moxifloxacin
Giddiness/vertigo/dizziness/headache	10	Kanamycin/Bedaquiline
Joint pain/leg pain/myalgia	9	Bedaquiline/Moxifloxacin/Pyrazinamide
Altered SGPT and SGOT	6	PAS/Bedaquiline
Blurring of vision/red eye	5	Bedaquiline/Ethambutol
Hearing decrease	4	Kanamycin
Peripheral Neuropathy/weakness/mouth ulcer	4	Cycloserine/Linezolid
Excessive cry & mood fluctuation/irrelevant thought/memory impairment/slurred speech	4	Cycloserine
Diffuse hair loss	1	Bedaquiline
Fine tremors	1	Kanamycin
Itching	2	Kanamycin/Bedaquiline
Menorrhagia	1	Bedaquiline/Rifampicin
Septicemia, Skin eruption and Anorexia	1	Clofazimine/Linezolid
Death	14	–

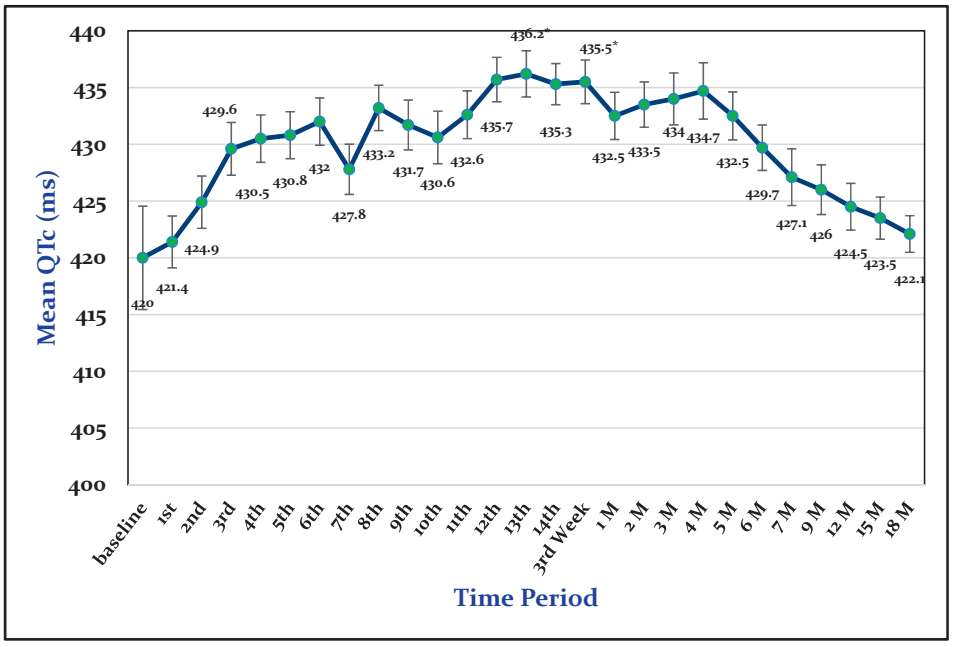

Fig. 2 – Mean QTc interval (ms) in BDQ treated DR-TB patients at different time interval (n = 127). *p < 0.0001 as compared to baseline, values are expressed as mean ± SEM (Paired student's'‘t’ test).

Table 3 – Comparison of mean increase QTc interval in patients treated with bedaquiline along with anti-TB drugs having potential effect on QT interval (n = 127).

Treatment with anti-TB drugs with potential to prolong QTc interval		Mean increase in QTc interval compare to baseline (ms)	p value
One drug (n = 4)	14th day	+9.5	0.3672
(Bedaquiline only)	3rd week	+12.75	0.2656
	3rd month	+23.75*	0.0356
	6th month	+20.75	0.0914
Two drugs (n = 48)	14th day	+10.81**	<0.0001
(Bdq + Cfz,	3rd week	+8.188*	0.0150
Bdq + Mfx, Bdq + Lzd)	3rd month	+5.152	0.1742
	6th month	+5.174	0.1211
Three drugs (n = 65)	14th day	+13.69**	<0.0001
(Bdq + Lzd + Cfz, Bdq + Lzd + Mfx)	3rd week	+16.18**	<0.0001
	3rd month	+18.44**	<0.0001
	6th month	+9.136*	0.0033
Four drugs (n = 10)	14th day	+24.50	0.2152
(Bdq + Lzd + Cfz + Mfx)	3rd week	+31.00	0.1111
	3rd month	+12.30	0.5092
	6th month	+19.90	0.3234

*p < 0.05 as compared to baseline, **p < 0.0001 as compared to baseline (Paired student's ‘t’ test).
Bdq = bedaquiline.
Lzd = linezolid.
Cfz = clofazamine
Mfx = moxifloxacin.

3.3.3. *BMI*

A significant increase of QTc interval (19.7 ms) was observed in patients having low BMI (<18.5 kg/m^2) ($p < 0.05$).

3.4. *Causality assessment of AEs*

Bedaquiline (50, 40.3%) was the most common causal drug responsible followed by linezolid (39, 17.1%), clofazimine (29, 12.7%) and ethionamide (27, 11.8%). Majority of AEs were categorized as possible in nature (196, 84.1%) followed by probable (33, 14.47%) as per WHO-UMC scale.

3.5. *Seriousness, severity and preventability of AEs*

Majority of AEs (107, 86.3%) were non-serious in nature. However, seventeen (13.7%) were serious which required hospitalisation (2), withholding BDQ temporarily (1) and death (14). According to clinical severity DAIDS grading, majority

were moderate (56, 45.2%) followed by mild (45, 36.3%), death (14, 11.3%), severe (06, 4.8%) and life-threatening (03, 2.41%). According to Schumock and Thornton preventability scale, 108 (87.1%) AEs were not preventable, while 16 (12.9%) were probably preventable.

3.6. *Efficacy of bedaquiline plus optimised background regimen*

3.6.1. *Body weight*

A periodical significant increase in mean body weight was observed at 3rd, 6th, 12th and 18th months of treatment in patients treated with BDQ plus OBR ($p < 0.001$, $p < 0.0001$) (Fig. 3).

3.6.2. *Sputum culture examination*

The median time for sputum-culture conversion was 40.89 ± 3.5 days (95% CI, 34–48 days). Out of 127 patients, 97 (76.38%) sputum cultures were positive at the enrolment. Out of these, 80 (82.4%) were converted into culture negative at the end of six months of BDQ treatment. While 83 (85.6%) and 88 (90.7%) patients were converted to sputum negative at twelve and eighteen months of post BDQ phase treatment respectively. While, 29 patients with baseline negative sputum culture remained negative throughout the study period (Figs. 4 and 5).

3.6.3. *Treatment outcome*

Out of the 127 patients, 102 (80.3%) had successful outcome. Remaining 25 unsuccessful (19.7%) patients include 14 (11.02%) death, 10 (7.9%) treatment failure and one (0.78%) defaulter.

3.7. *Impact of different variables on treatment outcome*

An attempt has been made to correlate different factors with treatment outcome. It was observed that early sputum culture conversion at 3rd month ($p < 0.0001$) and BMI (>18.5) ($p < 0.05$) were positive predictors of a successful treatment outcome. While low BMI (<18.5) ($p < 0.05$), smoking habit ($p < 0.05$) and overall combined personal habits (smoking/alcohol/tobacco chewing) ($p < 0.05$), bilateral or cavitary lesions ($p < 0.0001$) were negative predictors of successful treatment outcome (Table 4).

4. Discussion

The primary objective of this study was to acquire safety and tolerability data on BDQ in real life situation. The key findings confirm that BDQ containing regimen was well tolerated with modest QTc prolongation either alone and or in combination of other anti TB medications; however, none of the patient required permanent withdrawal of causal drug. Additionally, it has shown to be highly effective with fast sputum culture conversion rate with good treatment outcome.

Our study showed that majority of DR-TB patients were young (<30yrs.); similar to other studies.[7,8] Although, a study from South Korea differs with mean age more than 40 years.[9] This difference could be due to geographical variation in prevalence of disease, ethnic and racial variations and high survival age in the eastern countries. The high prevalence of DR-TB in young population is alarming as this would result in considerable health and financial burden on individual family and country. Secondly, all patients had previously received Category I, II & IV TB regimen. Similar findings have been reported in other studies.[10,11] This reflects progressive acquisition of drug-resistance mutants during sequential exposure to inadequate treatment leads to XDR-TB; thereby increasing the risk of DR-TB in treatment experienced patients.

In addition, mean body weight and BMI of DR-TB patients was low indicating that majority were '*undernourished*'. The baseline BMI of these patients was lower as compared to Guglielmetti L. et al[11] and Pym AS et al.[12]

Additionally, the sputum culture conversion rate was high similar to a retrospective study by Borisov SE et al;[13] but higher

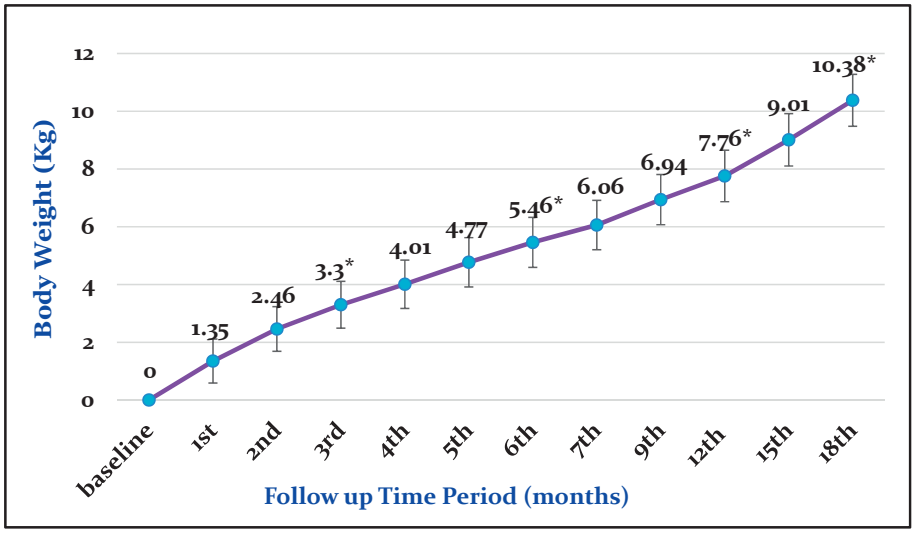

Fig. 3 – Changes of mean body weight in BDQ treated DR-TB patients at different time period(n = 127). *p < 0.0001 as compared to baseline, values are expressed as mean ± SD (Paired student's't' test).

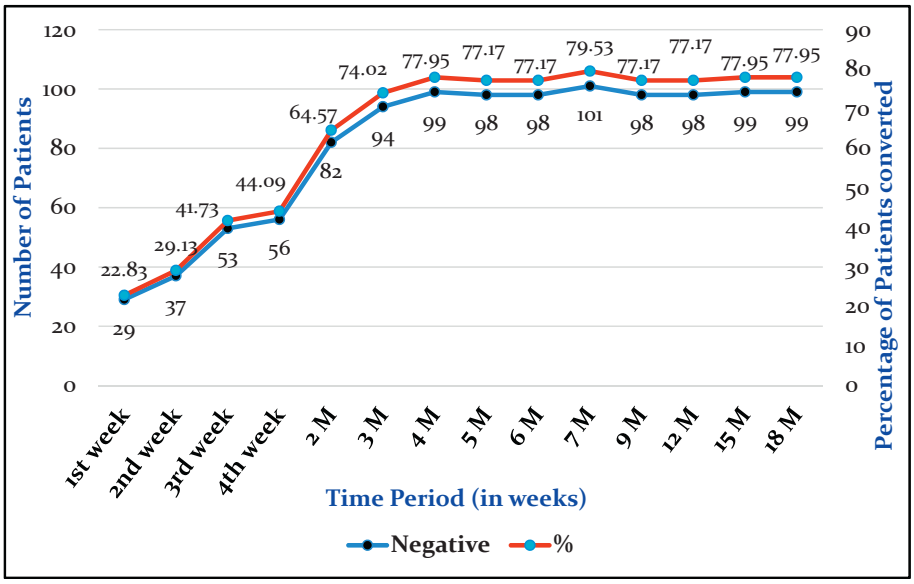

Fig. 4 – Median time for sputum culture conversion in BDQ treated DR-TB patients (n = 127).

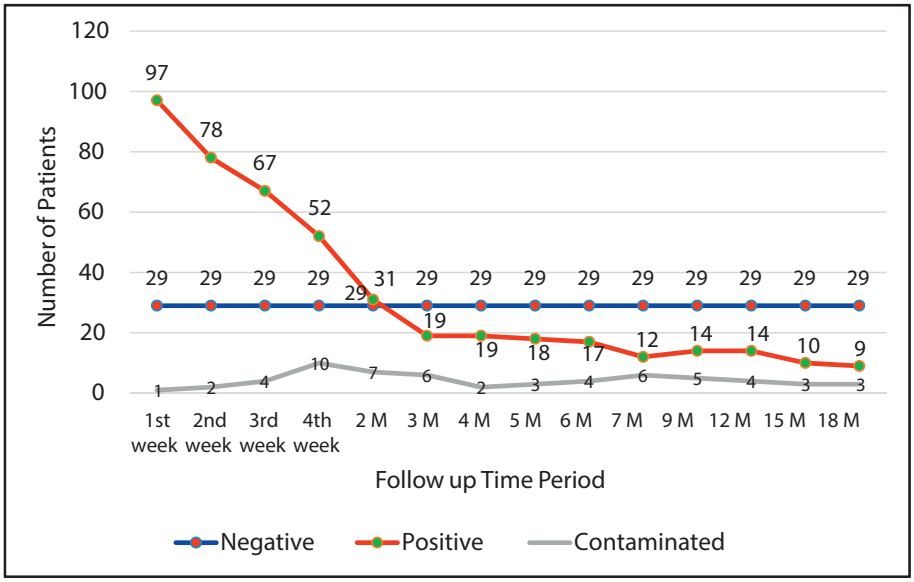

Fig. 5 – Sputum culture conversion in Bedaquiline treated DR-TB patients at different time interval (n = 127).

as compared to phase 2, multicentre trial by Pym AS et al[12] and randomized, double-blind, placebo-controlled, multicentric study by Diacon AH et al.[14] Bedaquiline in combination with linezolid has a promising role in presence of fluoroquinolone-resistant strains.[15] High sputum culture conversion rate (>87%) has been reported in MDR-TB patients treated with linezolid containing regimen.[16,17] In fact, 97% sputum culture conversion is reported in complicated MDR-TB and XDR-TB patients treated with BDQ.[18] More importantly, the median time for sputum culture conversion was as early as 40 days which is comparable to available literature.[7,13] Thus, the rate and time of sputum culture conversion was higher and faster in BDQ containing regimen. It can be stated that DST guided tailor-made regimen having bedaquiline along with highly active anti-TB drugs made a significant therapeutic difference for DR-TB patients in the study.

Further, almost half of the patients had bilateral infiltration with cavitary lung lesions at enrolment, which was considerably less as compared to other studies.[9] The extent of lung parenchyma and cavitary lesions has an association with treatment outcome.[3,10] Thus, the smaller number of patients having cavitary and bilateral lung lesions also contributed for high rate of successful outcome. The radiological extent of disease showing bilateral or cavitary lesions ($p < 0.0001$) were found to be negative predictors of successful treatment outcome.

Table 4 – Correlation of various factors associated with treatment outcome in DR-TB patients (n = 127).

Characteristic factors	Group I Successful (102, 80.3%)	Group II Not Successful (25, 19.7%)	p value
Gender			
Male	54	15	0.5254
Female	48	10	
Age (Years)			
≤40	83	21	0.7598
>40	19	04	
Body mass index (BMI)			
<18.5	71	23	0.0221*
≥18.5	31*	02	
Concomitant disease			
Yes	18	01	0.0864
No	84	24	
Personal habits			
Yes	47	17*	0.0495*
No	55	08	
Smoking			
Yes	27	12*	0.0365*
No	75	13	
Tobacco			
Yes	12	03	0.9739
No	90	22	
Alcohol			
Yes	8	02	0.9792
No	94	23	
Radiological extent of disease			
Cavitary lung lesion			
Yes	46	22**	0.0001*
No	56	03	
Bilateral/unilateral involvement			
Bilateral	49	23**	<0.0001**
Unilateral	53	02	
Culture conversion within 3 months			
Yes	93**	04	<0.0001**
No	09	21	

Values are absolute numbers. *p < 0.05 as compared to group I, **p < 0.0001 as compared to group I(Fisher's exact test).

4.1. *Treatment safety profile*

It is well known that second line anti-TB drugs are more toxic as compared to first line drugs.[19] The rate of AEs observed in our study is comparable to existing literature.[11–14] Probably, high rate of AEs could be due to active surveillance method and long term follow up.

QTc prolongation due to BDQ with highly active anti-TB medications has been a major concern to the prescribers and policy makers. Our study shows that Bedaquiline containing regimen definitely has a modest effect on QTc prolongation; synonymous with Diacon AH et al.[14] However, a small set of patients (10.24%), the QTc interval increment was higher than 60ms, albeit, it was certainly less as compared to studies by Guglielmetti L et al,[11,18] and Ferlazzo G et al.[20] While it was more than reported by Ndjeka N et al,[7] Pym AS et al[12] and Diacon AH et al.[14] This could be due to difference in number of patients treated with BDQ alone or concomitantly with two or three or four potential anti-TB medications having effect on QTc. However, an additive or synergistic effect on QTc interval cannot be ruled out. Further, majority of patients were underweight and dosage regimens were prescribed as per recommended weight band. Thus, the possibility of high dose of clofazimine, moxifloxacin and linezolid has been ruled out.

Surprisingly, five (3.9%) patients had clinically significant QTc prolongation (>500 ms). Of these, three were receiving clofazimine along with bedaquiline. Pym AS et al[12] has reported mean maximum change in QTcF interval 31.9 ms in patients treated with BDQ plus clofazimine as compared to 12.3 ms in those not prescribed clofazimine. In addition, Ndjeka N et al[7] observed significant increase in QTc with clofazimine. Thus, it can be stated that the rate, extent and risk of QTc interval prolongation increases with co-administration of clofazimine. QTc prolongation has been associated with co-administration of high dose moxifloxacin (800mg/day).[18] However, none of the patient received high moxifloxacin in our study.

Thus, bedaquiline plus OBR definitely prolongs QTc interval, albeit, the magnitude of prolongation varies in different studies conducted globally. Other variables such as gender, age, BMI, co-administration of one, two or three anti-TB drug(s) with potential effect on QT interval also determines the maximum QTc prolongation. Despite concomitant use of multiple QTc-prolonging drugs, it was a modest increase in QTc interval and none of the patient required discontinuation of treatment. However, this emphasizes the need for a through pre-treatment cardiovascular and biochemical evaluation as a preventive measure and for appropriate selection of patients for safe use of BDQ.

4.2. *Treatment outcome*

A substantial number of patients had successful treatment outcome in a short period. High success rates having been attributed to individualised treatment regimens.[21] Defaulter rate in present study (0.78%) was very low as compared to previous study.[8] Possibly, intensive follow-up and telephonic reminder to each patient decreased default rate. Comprehensive DST, accordingly tailor-made treatment regimens and negligible default rate contributed towards high successful outcome.

Interestingly, better treatment outcome was seen in young patients (<40 years). In elderly, damaged lung parenchyma due to smoking or age-related deterioration of health and low immunity negatively affects the outcome. Secondly, patients having high BMI had higher chance of successful outcome due to better nutrition and immunity. This indicates that better nutritional and immune status of patients improves outcome.[10]

Personal habits of smoking, tobacco chewing and alcohol consumption were found to be negative predictors of successful treatment outcome. Nicotine suppresses the immunity,[22] alcohol and smoking damages liver and lung respectively; disturbing drug metabolism thereby adversely affects the outcome. Overall mortality was low, comparable with the previous studies,[13,14] and even lower than WHO Global report, 2016 (27%). Individualised treatment regimens with close monitoring may have decreased number of deaths.

4.3. *Strength and limitations of the study*

This was a prospective study wherein the cohort was under active safety surveillance and the patients were followed up in post bedaquiline phase. An attempt has been made to determine the effect of different variables especially concomitant drugs on QTc interval. Additionally, the impact of various factors (patient, disease and drug) has been correlated with treatment outcome.

However, there were certain limitations. It was an observational open label single centre with absence of control arm and special populations in the study. Despite these limitations, we believe that the data generated in our study leads to certain important conclusions. The high and rapid sputum culture conversion rate, low mortality, absence of unexpected AEs indicates that BDQ based regimen was well tolerated and strengthened DR-TB treatment. Although, BDQ along with concomitant medications has the potential to prolong QTc, the benefit certainly outweighs the risk. The short-term safety data is reassuring, albeit, it is crucial to carefully evaluate pre-treatment cardiovascular system and closely monitor patients for QTc prolongation. Bedaquiline has the potential of becoming cornerstone drug of future tuberculosis treatment and maybe game changer for DR-TB treatment.

Declaration of Competing Interest

The authors have none to declare.

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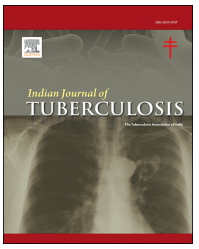

Nikshay Poshan Yojana (NPY) for tuberculosis patients: Early implementation challenges in Delhi, India

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ABSTRACT

Background: Nutrition support is one of the essential factors for envisioning Tuberculosis (TB) elimination in India by 2025. In this regard, Government of India introduced Nikshay Poshan Yojana (NPY) through Direct Benefit Transfer (DBT) as monthly financial assistance towards nutrition for TB patients in April, 2018. Assessment of early implementation challenges of the scheme is essential.

Objective: (a) To determine the number (proportion) of TB patients who received the benefits (b) to explore the challenges encountered by the health care providers in delivering the NPY through DBT (c) to explore the ways the incentives were utilised by the patients.

Material and methods: It was a cross-sectional study conducted among patients registered for TB treatment at Ladosarai and Mehrauli DOTS centre between July–September, 2018.Health providers engaged in implementation of NPY at the study sites were also interviewed. The data were collected through structured questionnaires, double entered and analyzed in Epi Data.

Results: Out of 119 patients registered, we interviewed 57 (47.9%) patients. Of which, 30 (52.6%) had received NPY for 2 months in the fourth and fifth month of treatment. The health providers reported increased workload, lack of training and complex reporting formats as main hurdles in implementation of the scheme. While, the patients cited non-availability of bank accounts and unlinked bank account with Aadhar card as difficulties to receive NPY through DBT.

Conclusion: Nearly half of the interviewed TB patients received nutritional incentives of NPY through DBT for 2 months. Non-availability of bank accounts and unlinked bank accounts were some challenges faced by both health providers and patient. It is recommended to address these implementation on time in order to reap the benefit of scheme in improving nutritional status of TB patients. Further studies are needed to determine the effect of nutrition support on TB patients.

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1. Introduction

Tuberculosis (TB) continues to be a major cause of mortality and morbidity in many countries worldwide.[1] As per Global TB report 2018, there were an estimated 10 million patients with TB in 2017 and 1.3 million died due to it. Ten countries account for 80% of incident cases of TB with India (27%) being at top among them. The estimated incidence of TB in India was approximately 2.8 million with 1400 deaths per day.[2] Evidently, India continues to be a high TB burden country.

Nutrition is considered to be intricately linked to development and outcomes of TB. The dual problem of malnutrition and TB creates a vicious cycle with TB leading to malnutrition and malnutrition predisposing TB. As estimated, 55% of TB incidence in India (more than 1 million new cases annually) is attributable to the effect of under nutrition and it is significantly greater than those to other attributable risk factors like smoking (11%), diabetes (9%) and Human Immunodeficiency Virus (HIV) (5%).[3,4] This implies that improving nutritional status could have dramatic impact on TB incidence.

In 2013, World Health Organization (WHO) recommended nutrition support integral to management of patients with TB.[5] Even, the End TB strategy endorses nutritional support to TB patients as an important component of patient-centered care.[6] Supporting nutrition to households with TB patients are in line with first three Sustainable Development Goals (SDGs) as well. Further, nutritional interventions have been associated with improved outcomes in TB patients such as reduced mortality,[7,8] improved weight gain9, earlier sputum conversion,[10] improved pharmacokinetics of key drugs,[11] improved functional status and adherence to therapy.[7]

The Government of India (GoI) has made a strong commitment to end TB by 2025, which would require concerted efforts and holistic management of factors influencing the prevention and control of TB.[12] In line with international recommendations, a novel step towards TB elimination has been undertaken by Revised National Tuberculosis Control Programme (RNTCP). RNTCP has developed a guidance document on TB and nutrition support. Escalating the initiative, the Government of India (GoI) has launched a scheme called "**Nikshay Poshan Yojana"(NPY)** which provides monthly financial incentive to improve the nutritional practices of TB patients.[13] The scheme was launched in April 2018 and it aims to provide INR 500 (~7USD) per month to all the TB patients till they complete their treatment. The incentive will be debited directly to their bank accounts which are linked to Aadhar (a unique identity number given for every citizen) through Direct Benefit transfer (DBT).[13] DBT is a mechanism of transferring subsidies directly to the people through their bank accounts to bring transparency, reduce leakages, delay, and terminate pilferage. The GoI is implementing DBT for more than 400 schemes in other sectors which includes nine schemes from the health sector.[14]

Though, it is early to study the implications of this scheme on nutrition status of patients with TB, we aimed to determine the number (proportion) of TB patients who received the benefits, their ways of utilization and explore the early implementation challenges in delivering NPY through DBT by health care providers and TB patients registered at a TB hospital in Delhi under RNTCP three months of its launch.

2. Methods

Study design: It was a cross sectional study and the data were collected from the RNTCP records and reports and through interviews of patients and health care providers using structured questionnaire.

Study Settings: The study was conducted in National Capital Territory (NCT) of Delhi. Delhi being the capital has a huge population influx with a total population of 16.8 million. Almost 20% of its population resides in slum areas which are overcrowded, thereby predisposing them to infectious diseases like tuberculosis. Delhi has 25 chest clinics and the TB hospital is one such chest clinic, covering 0.8 million population. The selected chest clinic has two Tuberculosis units (TUs) and 8 Designated microscopy centres (DMCs) with attached DOTS centre. All TB patients diagnosed and treated here are registered on the NIKSHAY portal. The Nikshay Poshan Yojana (NPY) through DBT is being implemented at the chest clinic since the inception of the scheme. Senior TB supervisors (STS), Medical officer TB control (MO-TC) and District TB Officer (DTO) are involved in the process of identifying, validating and disbursing the financial incentives through DBT.

2.1. *Process involved in delivering NPY using DBT*

All patients diagnosed with TB are asked to furnish the bank details which includes the account holders' name, account number, IFSC code and Aadhar number for authentication. The STS ensures the notification of TB patients in NIKSHAY (a TB notification web-portal from RNTCP) with complete address, mobile number, Aadhar number and bank details. If beneficiary does not possess Aadhaar, STS facilitates beneficiary for Aadhar enrolment at Aadhar enrolment centre located in the respective block or taluka or tehsil at a convenient location to the beneficiary. The health staff also helps in updating the Aadhaar number in TB Notification register placed at health facilities with signed copies of the same. The STS along with data entry operator (DEO) at district TB centre check for completeness of the details provided by the beneficiaries and the validated list is submitted to the MO-TC. The MO-TC ensures timely submission of check list of beneficiaries from STS/health staff through DEO. The MO-TC then submits the validated list to the DTO for further processing. The DTO ensures that all the MO-TCs of the district are submitting the validated beneficiaries list on time. The DTO is responsible for training of the health staff on DBT and ensuring regular electronic payment (e-payment) using DBT through Public Financial Management System (PFMS) of the programme. The State TB Officer is responsible for providing necessary directives, plan, review and ensure timely budget or funds for financial support of TB patients.[15]

2.2. Study sites

The study was conducted at two DOTS centres under the selected chest clinic covering a total population of 0.2million and the centres were purposively selected based on their workload. NPY was operational in the study site since April, 2018.

2.3. Study population

All patients with TB who were registered for treatment at the two DOTS Centres from 1st July to 30th Sept 2018 and willing to participate were included. All the key health care providers involved in the implementation of NPY through DBT were interviewed to explore the early implementation challenges.

2.4. Study tool

Structured questionnaires were designed to collect the information on utilization of NPY from patients who had received incentives through DBT and explore the challenges in implementation of NPY through DBT from key programme staff. The pre-tested study tool for patients comprised of three sections. The first section included nine questions namely socio-demographic characteristics such as Nikshay ID, age, gender, education, occupation and clinical characteristics like type of TB, date of start of treatment, category of TB treatment and TB outcomes (if available). The second section included six questions on the possible reasons for receiving or not receiving the benefit under NPY through DBT. The third section included three questions pertaining to utilization of the nutrition incentives and patients' perception about NPY.

The pre-tested study tool for health providers comprised of two sections. The first section constituted questions pertaining to designation of the programme staff; years of experience in TB control programme. The second section had six questions to include enabling factors and challenges in implementation of the NPY.

2.5. Data variables

A list of all TB patients (from 1 July 2018 to 30 September 2018) was prepared based on the information from the TB laboratory register (DMC), TB treatment register of the chest clinic and NIKSHAY.

Data on socio-demographic (age, gender, education and occupation) and clinical (number of patients who received incentive through DBT, type of TB, category of treatment and TB outcomes if available) were obtained from the TB register, DBT register, treatment cards. Reasons for receiving and not receiving the financial incentive and ways of utilization of incentive amongst those who received it, were explored through patient interviews using structured questionnaire. Challenges as perceived by the programme staff, programme managers and patients during the process of linking with DBT under NPY were elicited through patient and health provider interview using structured questionnaire.

2.6. Data analysis

The data were double-entered, validated and analyzed using Epi Data version 3.1 for entry and version 2.2.2.183 for analysis (Epi Data Association, Odense, Denmark). Descriptive analysis was performed in the form of mean and SD or proportions wherever appropriate. Statistical difference between means was calculated using the independent t test. The chi square test/fischer exact test was used to analyze the difference between proportions. P value < 0.05 was considered statistically significant, in finding factors associated with receiving financial incentives for nutrition support.

2.7. Ethics

Ethics approval was obtained from the Institutional Ethics Committee of the NITRD, New Delhi, India and the Ethics Advisory Group of the International Union Against Tuberculosis and Lung Disease, Paris, France. Written informed consent was taken from the patients and health care providers. The consent form had two parts: Patient information sheet and the consent form, which was signed by the participant. Confidentiality and privacy of the study participants were maintained.

3. Results

During the study period, there were 119 patients registered for TB treatment; 40 were registered at Ladosarai and 79 patients were registered at Mehrauli DOTS centre. Out of these only 57 (47.9%) could be contacted as 30 patients were found to be shifted to other DOTS centre, 20 had provided wrong address, 11 refused for interview and 1 patient had died. Of the 57, only 52.6% (30) had received NPY incentive. Among the 30 received who received the incentive, 12 patients received the amount during their fourth month of their treatment and 18 received during fifth month. None of the patients had received the NPY incentives for the entire course of the treatment (Fig. 1).

There was no significant difference in the mean age of those who received NPY incentive from those who did not (mean age of participants receiving NPY $= 31.8 \pm 11.0$; mean age of participants not received NPY $= 29.9 \pm 12.6$; $p = 0.54$).

Majority of the participants belonged to 15–44 years age group ($n = 44$; 77.2%). There were 16 male and 14 female patients with TB who had received NPY incentive while 22 male and 5 female patients did not receive it. A large proportion of study participants ($n = 42$; 73.7%) were diagnosed with pulmonary TB. There were 27 patients in treatment Category I and 3 in treatment Category II who received NPY incentive. Overall there was no significant statistical difference in clinico–demographic profile of the participants who received the incentive from those who did not (Table 1).

All patients received their nutrition incentive during last months of continuous phase of treatment and therefore reported its non-utilization.

Three key health providers were interviewed to explore the challenges they faced in implementation of NPY. All three of

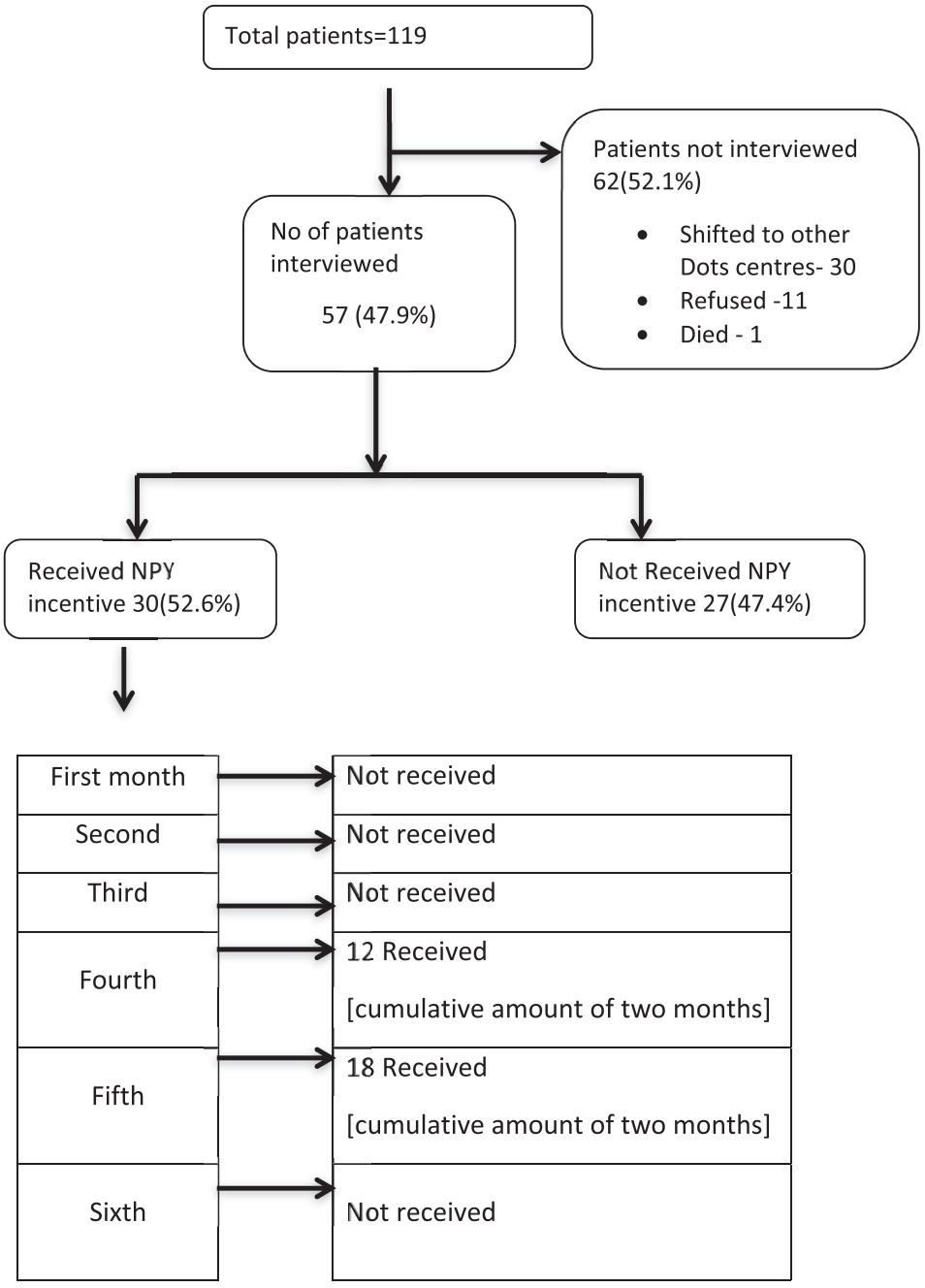

Fig. 1 – Flow of registered patients with TB and receiving NPY incentive during July–Sept 2018 at Chest Clinic, New Delhi.

them reported increased workload and complex reporting formats as main hurdles in implementation of the scheme. On the other hand, patients cited non-availability of bank accounts and unlinked bank account with Aadhar number as difficulties in receiving NPY through DBT. While health providers suggested training of human resource, increase in human resource and sharing of workload as possible solutions to the challenges, the patients recommended disbursing the amount through other modes like cash, vouchers and food items would be beneficial (Table 2).

4. Discussion

It is one of the first study conducted in Delhi to understand the utilization and elicit the challenges in implementation of NPY. Our study findings suggest that one in two interviewed TB patients are beneficiaries of NPY. The major challenges for implementation are increased workload as perceived by the health care providers and non-availability of Aadhar linked bank accounts for patients. Understanding the challenges of

Table 1 – Demographic and clinical profile of the registered patients at DOTS centres of the selected chest clinic, New Delhi (July–September 2018).

Variables	Received NPY incentive (n = 30)	Not Received incentive NPY (n = 27)	Total (n = 57)
	Number (%)	Number (%)	Number (%)
Age			
<15 years	0 (0)	1 (3.7)	1 (1.7)
15–44 years	24 (80)	20 (74.1)	44 (77.2)
45–64 years	6 (20)	6 (22.2)	12 (21.1)
Gender			
Male	16 (53.3)	22 (81.5)	38 (66.7)
Female	14 (46.7)	5 (18.5)	19 (33.3)
Type of TB			
Pulmonary	22 (73.3)	20 (74.1)	42 (73.7)
Extra-pulmonary	8 (26.7)	7 (25.9)	15 (26.3)
Treatment Category			
Category I	27 (90)	19 (70.4)	46 (80.7)
Category II	3 (10)	5 (18.5)	8 (14.1)
Category IV	0 (0)	2 (7.4)	2 (3.5)
Category V	0 (0)	1 (3.7)	1 (1.7)

Table 2 – Challenges faced and solutions offered by health providers and patients with TB for implementation of NPY.

Study Participants	Challenges	Solutions
Health Providers	Increased work load; Lack of trained human resource; Complex reporting formats	Increase Human resource; Training of existent manpower; Sharing workload on rotational basis
Patients	No bank accounts Aadhar card not linked with bank account Delay in transfer incentive to bank account	Disbursing the amount through other modes like cash, vouchers and food items.

implementation is crucial in the context of improved nutrition thereby impacting the treatment outcomes.

Our study suggests that 52.6% (n = 30/57) of the total interviewed patients received nutrition incentive under NPY and that too during fourth and fifth month of their treatment. None of the patients had received timely incentive for the entire course of treatment. This is not in line with the suggested schedule of payment where in first incentive is to be paid on notification of the case while last incentive at the end of treatment. The possible reasons for this could be non-availability of bank accounts, delay in submission of bank details and verification procedures by DTO.[16] Also, linking of NIKSHAY with Aadhar is imperative for smooth implementation of DBT. Due to delay in receiving payment, none of the patient could utilize it for nutrition support, defeating the purpose of the scheme. This has important policy implications as policy makers need to relook at method of disbursing the incentive.

The Aadhar linked bank account was an important requisite for this benefit to be availed by patients. However, most of the TB patients are from migrant communities living in urban slums of Delhi and did not have Aadhar card. Also, people belonging to vulnerable populations at risk of TB such as intravenous drug users, commercial sex workers or destitute do not have valid identity proof which makes the process of obtaining Aadhar card more cumbersome. Owing to the absence of Aadhar card, disbursements through other modes such as cash, vouchers and food items were suggested by patients with TB in the current study. However, there is equivocal evidence about effectiveness of different forms of economic interventions on TB incidence and its treatment outcomes. Further, providing financial assistance to patients with substance use and alcohol may encourage them to continue these malpractices and thereby directly affecting the treatment outcomes.[17]

Several challenges such as increase in workload or additional burden of making disbursements, lack of training of the involved staff regarding implementation of NPY were reported by the providers. Training and re-training of the existent staff and sharing of workload are some possible solutions suggested by health providers and have been documented as proven interventions for effective delivery of health services.[18]

The study has its strengths and limitations. The strengths are (a) the study was conducted under programmatic settings and depicts the ground reality of the programme implementation (b) the interviews were conducted by non-programme implementers and has least bias. The limitations are (a) The study was conducted in two DOTS centre attached to the chest clinic in Delhi. The level of training, knowledge amongst providers and type of patients may be very different from other populations. Hence, the findings should be generalised to other settings with caution (b) that the challenges of the scheme were assessed during the first

year of its implementation, which are true for any other public health schemes the early implementation challenges are expected to some extent.

5. Conclusion

Nearly half of the interviewed TB patients received nutritional incentives of NPY through DBT. Non-availability of bank accounts and unlinked bank accounts were some challenges faced by both health providers and patients. It is recommended to address these implementation challenges on time in order to reap the benefit of scheme in improving nutritional status of TB patients. Further studies are needed to determine the effect of nutrition support on TB patients.

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Conflicts of interest

The authors have none to declare.

Authors' Contribution

RK: Principal Investigator and corresponding author, conception / design of the protocol, acquisition of data, data analysis / interpretation, drafting / critically reviewing the paper, giving approval for the final version to be published,
NS, KUK: design of the protocol, data interpretation, critically reviewing the paper, giving approval for the final version to be published,
TA: conception / design of the protocol, data analysis / interpretation, critically reviewing the paper, giving approval for the final version to be published,
SBN: design of the protocol, data interpretation, critically reviewing the paper, giving approval for the final version to be published
KS: Designing of study tool, data analysis/data interpretation, critically reviewing the paper, giving approval for the final version to be published
RS: design of the protocol, data interpretation, critically reviewing the paper, giving approval for the final version to be published

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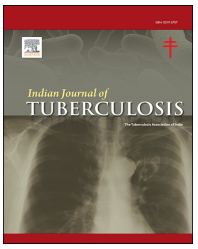

Review article

Literature review of oral tuberculosis and report of a case with unique histological presentation

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ABSTRACT

As a consequence of the emergence of drug resistant tuberculosis (TB) and various immuno-compromised states, there is a re-emergence of many forgotten extrapulmonary manifestations of TB including oral TB, which must be taken into consideration while diagnosing oral lesions. The present article discusses the geographical burden, temporal evolution, demographic variables, clinical presentation and treatment of oral TB. The occurrence is most commonly secondary to pulmonary TB but oral symptoms may precede systemic symptoms. The most common presentation is ulceration (71%) and histopathological specimens demonstrate the characteristic epithelioid and langhans cells. In a unique case, presented here, an ulcerative tuberculous gingival lesion demonstrated dense plasma cell infiltration histologically and closely mimicked plasma cell gingivitis which made the diagnosis challenging.

1. Introduction

Tuberculosis (TB) is a chronic, infectious granulomatous disease caused by *Mycobacterium tuberculosis* and less frequently by *Mycobacterium bovis* and atypical mycobacteria.[1] It ranks among the top 10 causes of death world-wide.[2] India accounts for nearly one third of the global burden of TB.[3] The average prevalence of all forms of the disease in the country is estimated to be 5.05 per thousand and average incidence of smear-positive cases, 84 per lakh.[4]

Morgagni reported the first case of oral TB seen as lingual involvement in 1761. Based on reviews published before 1950, oral TB accounted for 0.1–5% of all TB infections. With advances in chemotherapy and improvement in public health and hygiene, the rate deteriorated. However, nowadays, oral manifestations are re-appearing alongside many forgotten extrapulmonary infections as a consequence of the

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emergence of drug-resistant TB and the emergence of Acquired Immuno-deficiency Syndrome (AIDS)[5]

Oral TB rarely occurs as a result of primary inoculation and invasion of mycobacteria owing to the cleansing effects of saliva, the relative paucity of lymphoid tissue and the action of antagonist commensals. It occurs more commonly, secondary to pulmonary TB, which leads to increased concentration of mycobacteria in the oral cavity. A breach in the oral mucosa as a result of tobacco use, traumatizing dentures or poor oral hygiene leads to localization of the mycobacteria and infection. Pathogenesis also includes hematogenous spread of infection. In a rare case, the Bacillus Calmette–Guérin (BCG) vaccination has been reported as a possible precursor for tubercular osteomyelitis of the hard palate.[6]

Oral TB may manifest as ulceration, swelling, granulomatous plaques and nodules. The varied presentation, similarity in clinical morphology to other oral conditions and rarity of occurrence make the diagnosis of oral TB challenging. The present article seeks to review the prevalence and presentation of TB in the oral cavity and also report a unique case of gingival tuberculosis, histologically mimicking plasma cell gingivitis, another rare condition of the oral cavity that occurs as a hypersensitivity reaction to antigens sourced in food flavoring agents and spices.

2. Review of literature

2.1. Global burden and geographical distribution

Although the number of deaths due to TB is declining globally, it still remains one of the top ten causes of death worldwide. In 2015, the last year for which the World Health Organization (WHO) published estimates for all causes of death, TB ranked as the ninth most common cause of death. From 2012 to 2016, it was the number one cause of death from a single infectious agent, ranking above HIV/AIDS. Three WHO regions accounted for 87% of new cases in 2016: South-East Asia (45%), Africa (25%), and the western Pacific (17%). The European region and the Americas each accounted for 3% of the total, with the remaining 7% in the eastern Mediterranean region. Of these, India accounted for 27% of the cases. Fig. 1 shows an estimated country-wise incidence of TB in 2016.[7,8]

Most published cases of oral TB are reported from South-East Asia region, which as described earlier, also accounts for the highest incidence of TB. This is followed by the European region and the Western Pacific region. The countries from which cases of oral TB have been most commonly reported are India, China, Brazil and Turkey.[9] However; this may not report the true incidence of oral TB as lack of technology in the developing countries may prevent accurate and comprehensive reporting.

2.2. Temporal evolution

According to Popescu et al, the oral cavity involvement in TB is very rare in relation to the period of time, with a mean of three cases reported every five years and a relatively stationary trend of the incidence.[9]

2.3. Demographic data

Andrade et al studied 46 cases of oro-facial tuberculosis over a period of 16 years and reported no gender predilection (M: F = 0.917) and a wide age range of occurrence, the most common age group being 11–30 years.[10] However, other reviews report a mean age of 45 years and a definite gender distribution (M: F = 1.5–2:1). It is also reported that TB lesions were encountered more frequently in men in the buccal mucosa and the tongue whereas the gingiva was most frequently involved in women.[5,9] Most patients are unaware of their disease status when they report with oral manifestations. In approximately 50% of patients, an oral manifestation of TB has led to the diagnosis of the previously unknown systemic infection.[11]

2.4. Types of infection

An oral tuberculous lesion may be primary or secondary.[12] Primary lesions occur when oral inoculation occurs first and there is no concurrent pulmonary involvement. They are extremely rare such that published literature about primary lesions exists only in the form of case reports. Secondary oral lesions, a form of extra-pulmonary TB, occur more commonly and demonstrate primary foci in the lungs with a subsequent oral involvement. Table 1 describes the features and differentiating characteristics of the two types of TB infection.

2.5. Clinical presentation and differential diagnosis

Tongue is most frequently involved in oral TB. The dorsal aspect is most frequently affected closely followed by the lateral borders. In India, lingual involvement with the disease has been found to be 0.8% of all total tongue pathologies.[13]

The buccal mucosa is more commonly associated with primary oral infection while in secondary infection; the lips and gingiva are more frequently involved. Salivary glands (with a predominance of the parotid gland), hard and soft palate, floor of the mouth and the mandible may also be affected in orofacial TB.

Morphological presentation of oral tuberculosis in more than 40% of cases is described as a typical ulceration, superficial or deep, with irregular margins, undermined edges and a granulating floor. It tends to increase in size slowly and, sometimes, may be ragged and indurated. The appearance of satellite lesions is rare. Infrequently, an oral TB lesion may appear as a non-tender swelling, a nodular mass or diffuse granulomatous enlargement. Table 2 depicts the various manifestations of oral TB reported in literature from 1950 to 2009.[5]

Recent cases reported in literature also demonstrate a similar trend with 71% of oral TB lesions manifesting as ulceration. A review of 13 case reports from of oral TB from 2010–18 is presented in Table 3.[14–26]

Although the clinical picture of oral TB is variable and non-specific, the most common presentation is ulceration. Therefore, a complete medical history, clinical examination and accessory investigations must be undertaken to differentiate a tuberculous ulcer from other diseases that present as ulcers during their course. Table 4 summarizes a list of such

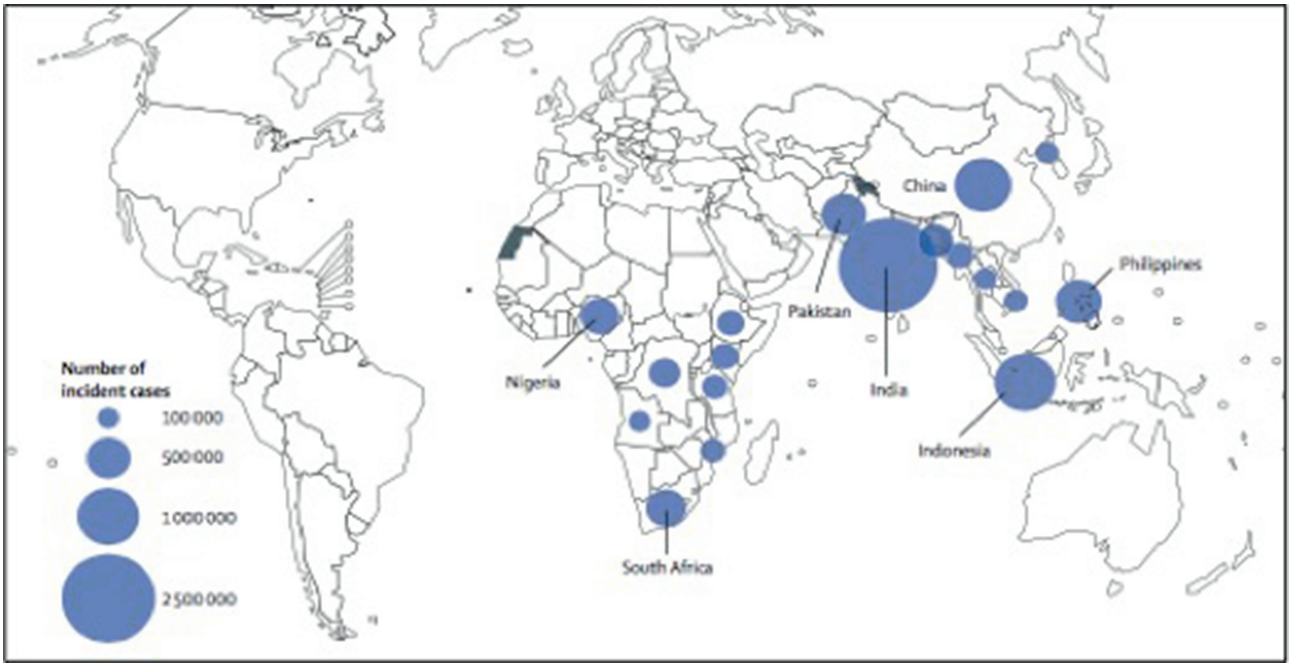

Fig. 1 – Estimated country-wise incidence of Tuberculosis in 2016.

Table 1 – Occurrence, risk factors, clinical picture and management of the primary and secondary forms of oral TB.

Variable	Primary oral tuberculosis	Secondary oral tuberculosis
Occurrence	Rare, found predominantly in children	More common, affects the middle aged
General and local risk factors	Immunodeficiency (e.g. in diabetes, neoplasms, alcoholism, states after graft procedures, HIV infection, prolonged steroid therapy), tobacco smoking, oral mucosa traumas, hyperkeratotic disorders, poor oral hygiene, periodontitis	
Clinical Manifestation	Ulcer – superficial and covered with granular tissue	Ulcer – with undermined, irregular edges
Pain	Lesion is not painful	Painful
Lymph nodes	Enlarged and painful	Enlarged and not painful
Management	Elimination of traumatic factors and anti-tubercular therapy	

diseases with their identifying features to aid in proper diagnosis.[12,27,28]

2.6. *Diagnostic tests and treatment*

Table 5 describes the various tools that aid in the diagnosis of oral TB along with their advantages.[29]

Treatment for oral tuberculosis is undertaken in consultation with a physician and the importance of treatment completion and regular follow up must be explained to prevent development of drug resistant tuberculosis and recurrence. Anti-tubercular therapy comprises of isoniazid (10 mg/kg of body weight), rifampicin (10–20 mg/kg of body weight) and pyrazinamide (10–20 mg/kg of body weight) for two months followed by isoniazid and rifampicin for the following four months.[3] Complete resolution of oral lesion usually occurs with systemic therapy and conservative localized management and more aggressive treatment options are not required.

Diagnosis and treatment of oral tuberculosis are not just challenging but also crucial because of its highly infectious

Table 2 – Macroscopic manifestations of oral TB reported in literature from 1950 to 2009.

Manifestation of oral tuberculosis lesions	Percentage of reported patients (in %)
Ulceration	55
Swelling	24
Discharge	10
Nodules (Tubercles)	8
Extraction socket involvement	5
Granulomatous plaque	4
Diffuse inflammation	2

Table 3 – Macroscopic manifestations of oral TB reported in literature from 2009 to 2018.

Manifestation of oral tuberculosis lesions	Percentage of reported patients (in %)
Ulceration	71.4
Granulomatous Enlargement	21.5
Nodules	7.1

Table 4 – Differential Diagnosis of ulcerative oral lesions.

Oral disease	Number of ulcers	Associated pain	Course and duration	Clinical presentation
Oral TB	Single	Primary- No pain Secondary- Painful	Chronic ulcer with other constitutional symptoms of TB	Ragged, indurated and irregular margins
Traumatic Ulcer	Single	Painful	Spontaneous healing after elimination of traumatic factor	Inflamed basis, shallow or deep ulcer, margins slightly elevated
Recurrent Aphthous Stomatitis	Single/Multiple	Painful	Recurrent ulcers, spontaneous healing after 7–30 days	Shallow ulcer, inflamed halo
Syphilis	Single	Not painful	Ulcer lasting for 2–6 weeks, spontaneous healing	Smooth, indurated margins
Ulcerative Lichen Planus	Single/Multiple	Painful	Recurrent ulcers, may be preceded by sub-epithelial bullas	Shallow, vast ulcer, Wickham's striae present
Planoepithelial carcinoma	Single/Multiple	Initially not painful, becomes painful later in course	Chronic ulcer, developing slowly	Irregular margins, indurated base, cauliflower-shaped overgrowth possible

nature and the frequent absence of concomitant systemic symptoms. The diagnosis becomes even more difficult if the lesion mimics another disease entity. Cases of oral TB clinically resembling a traumatic ulcer and squamous cell carcinoma have been reported in literature.[30,31] The following discussion reports a case of oral tuberculosis histologically resembling plasma cell gingivitis.

3. Case report

An 18-year old female patient was referred to the Department of Periodontology for evaluation and treatment of an unusual ulcerated lesion on the maxillary labial gingiva. The patient reported noticing a painful ulcer in her upper front gums one month ago. She visited a nearby dentist for the same and was prescribed a local gum paint application that she was using three times a day for last 20 days. Over the ensuing days, the lesion became larger and more widespread, was slightly painful and bled occasionally.

The patient gave no history of fever or weight loss but reported feeling generally unwell for the last one month. On examination, the patient appeared to be pale, frail and irritable. Extra-oral examination revealed no abnormality except small palpable submandibular lymph nodes on the right side.

Intra-orally, an ulcerated, irregular, ill-defined granular lesion was seen on the maxillary labial gingiva. It involved the gingiva in relation to the four incisor teeth laterally and extended from the gingival margin into the alveolar mucosa apico-coronally. The lesion bled on provocation. Multiple soft tissue perforations or gingival dehiscence resembling sinus openings were present near the mucogingival junction. The left central incisor was present in a cross bite relation and grade II mobility was observed in both the central incisors (Fig. 2).

An intra-oral periapical radiograph and routine blood investigations were advised for the patient. Due to pain and bleeding, she was not brushing in the region therefore, oral hygiene instructions were given and regular maintenance was encouraged.

The IOPA revealed interdental bone loss between the two central incisors (Fig. 3). Blood investigations depicted an increased Erythrocyte Sedimentation Rate (ESR) measured using the Wintrobe's Method; up to 64mm in the first hour and decreased Hemoglobin level i.e. 9g/dl. An incisional biopsy was planned for the patient.

The biopsy was taken from the gingiva in relation to right central incisor without involving the lesion on the left side. The area was irrigated with saline and the patient was asked to report after 1 week. In the follow up visit, it was observed that the area exhibited delayed healing.

The histopathological report revealed a dense infiltration of plasma cells in the connective tissue. While other chronic inflammatory cells were present too, they were in lesser numbers. The histopathological diagnosis was, therefore, plasma cell gingivitis (Fig. 4a and b).

In keeping with the diagnosis, the patient was strictly instructed to stop gum paint application, maintain good oral hygiene and report after one month.

Table 5 – Diagnostic tools for diagnosing oral TB.

Diagnostic tool	Advantage
Heaf Test	Easy interpretation; less inter-observer variability
Mantoux Test	Screening test, diagnosis of active TB, more precise than radiograph
Radiograph	Easy to perform
Ziehl – Neelson staining	Simple, non-invasive, economical
Auramine Fluorescence	More sensitive, quick results, contrast enables better visualization
ELISA	More sensitive, faster
LJ medium culture	Less expensive than BACTEC
BACTEC	Differentiates M.tuberculosis from other species
PCR	Sensitive, quick results

ELISA: Enzyme-linked Immunosorbent Assay, LJ: Lowenstein-Jensen, PCR: Polymerase Chain Reaction.

After one month, the lesion did not show any signs of improvement. However, this time the patient reported developing cough since the last 20 days. Hence, a chest X-ray was advised.

The radiograph revealed a consolidation in the lower lobe of the right lung (Fig. 5). The patient was referred to a physician who confirmed pulmonary tuberculosis and prescribed Directly Observed Treatment Short Course (DOTS) regime for 6 months according to the regimen described above. She was also advised a monthly visit to the Department of Periodontology to follow up on the oral lesion.

One month after the start of therapy, the lesion showed improvement. The biopsy site appeared to be healing well. Mobility in the central incisors had reduced to grade I and the submandibular lymph nodes were no longer palpable. Complete resolution of the oral lesion occurred 6 months after the onset of treatment (Fig. 6).

4. Discussion and conclusion

The present case report describes a unique case of oral tuberculosis with histological resemblance to plasma cell gingivitis. Plasma cell gingivitis is an uncommon benign inflammatory condition of unclear etiology. It was first reported in the early 1970s as plasmacytosis of the gingiva. It has been hypothesized that an immunologic reaction to some allergic antigen might be the possible causative agent. Mint in the toothpaste, chewing gum, cinnamon aldehyde, strong spices, chilies, chewing of khat, and certain constituents of herbal toothpastes have been documented as the reported allergens. The most common clinical presentation is an inflammatory; either generalized or localized erythematous, edematous, macular lesion with cobblestone/nodular or velvety appearance with a sharp demarcation at the mucogingival junction.[32]

The present case did not show the characteristic erythematous lesion of plasma cell gingivitis but a history of use of gum paint, a possible allergen, and histological demonstration of dense plasma cell infiltrates directed the diagnosis towards this rare inflammatory condition.

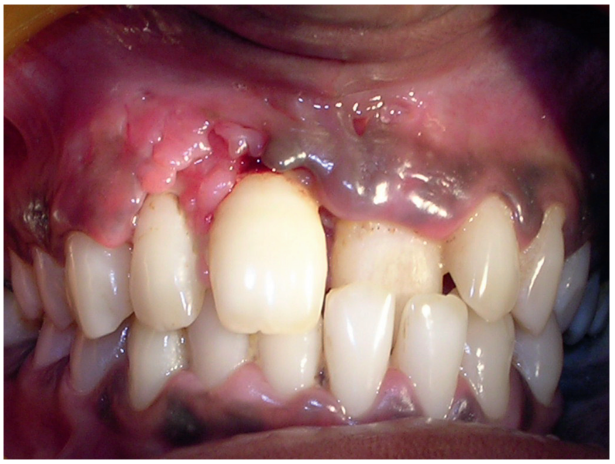

Fig. 2 – Pre-treatment clinical presentation of an ill-defined, irregular ulceration in relation to gingiva of maxillary anterior teeth more pronounced in 11 and 12 region.

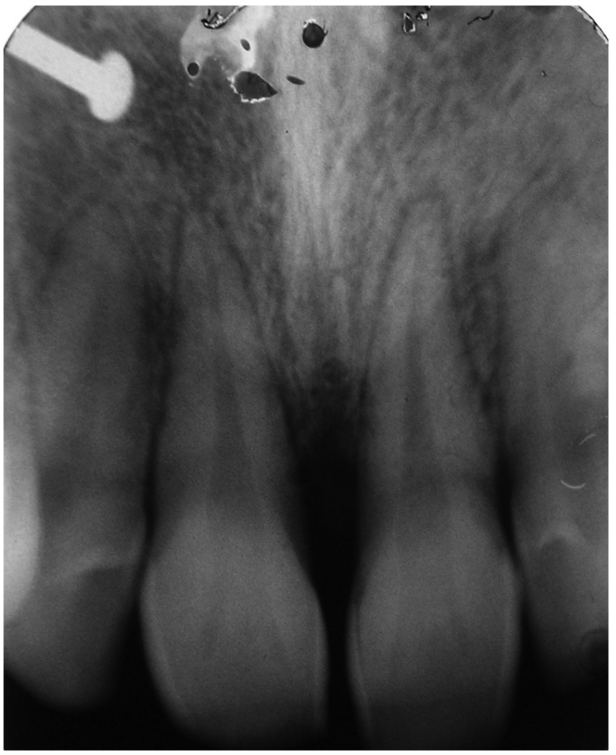

Fig. 3 – Intra-oral Periapical Radiograph showing bone loss in the interdental region in relation to 11 and 12, and 11 and 21.

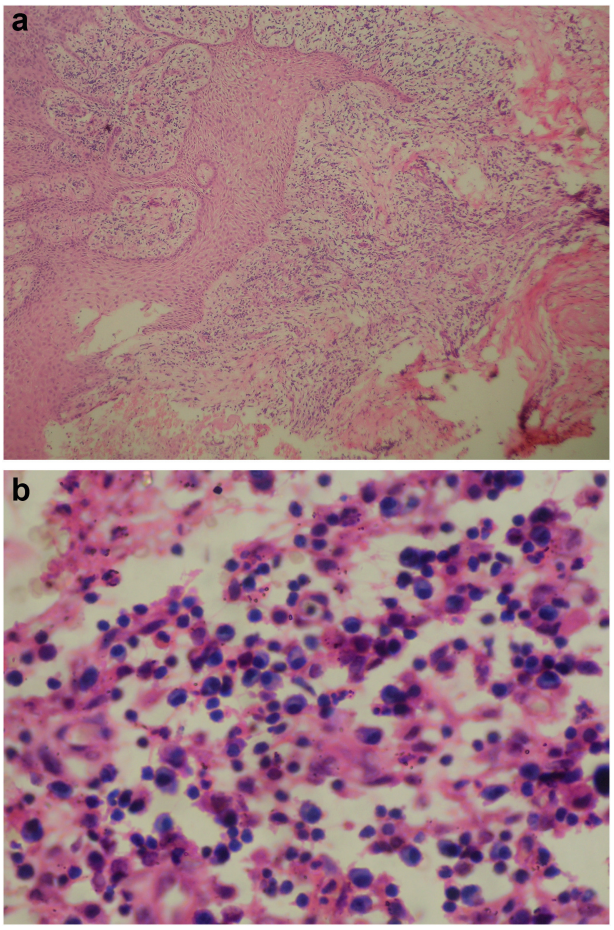

Fig. 4 – a: Photomicrograph showing the presence of a stratified squamous, parakeratinized epithelium and a dense aggregate of chronic inflammatory cells in the sub-epithelial connective tissue at a magnification of 10X. b: Photomicrograph showing densely infiltration of connective tissue with plasma cells seen as large, basophilic cells with eccentrically placed nuclei at 40X magnification.

Therefore, the patient was instructed to stop the use of gum paint and maintain good oral hygiene, as the management of plasma cell gingivitis is symptomatic and only directed towards the elimination of allergic or predisposing factors.[20]

However, when no improvement was seen one month later and the patient reported development of cough, the diagnosis was reconsidered. The diagnosis of tuberculous gingivitis was confirmed with a chest x-ray and anti-tubercular therapy initiated with a favorable response.

The present report describes a case of oral tuberculosis with the usual morphological manifestation of ulceration but unique histological findings, which may be attributed to superimposition of the hypersensitivity reaction masking the usual features of presence of epithelioid cells and Langhans giant cells.

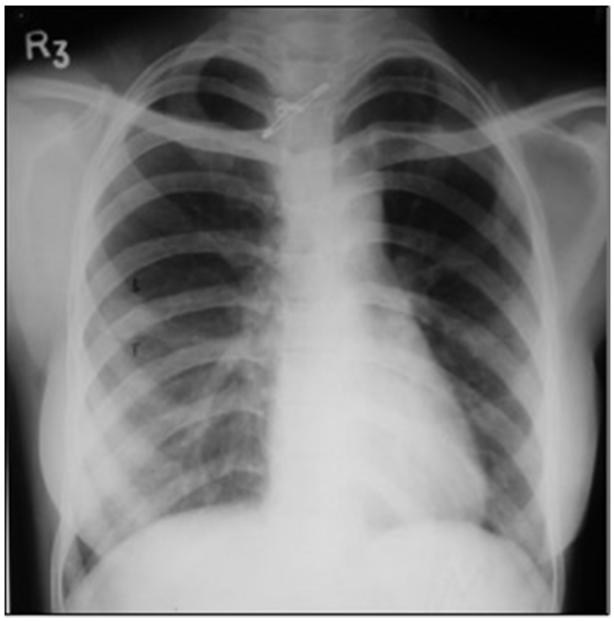

Fig. 5 – Chest X-Ray showing consolidation in the lower lobe of right lung.

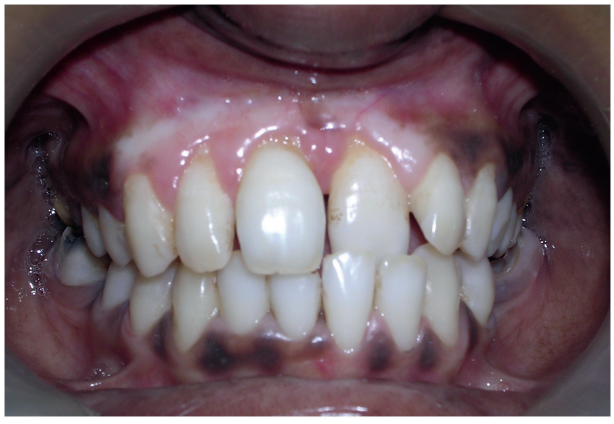

Fig. 6 – Clinical presentation showing complete resolution 6 months from the start of therapy.

Ethical approval

This article does not contain any studies with animals performed by any of the authors. All procedures performed were in accordance with the Ethical standards of the Institutional Research Committee and with the 1964 Helsinki Declaration and its later amendments.

Informed consent

Informed consent was obtained from the patient.

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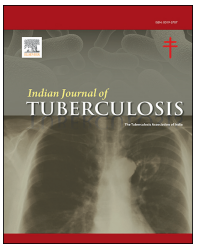

Review article

Tuberculosis in 2019

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ABSTRACT

Tuberculosis (TB) updates and guidelines have been published rapidly in last few years. The WHO and RNTCP have recommended suggestions that have changed the diagnostics and therapeutics paradigm in 2019. The rapid nature of these changes need to be appraised at the pulmonologist end. We conducted a google survey to study these gaps and subsequently review TB in 2019 focusing on the gaps in the survey. We narrate a short review covering the important diagnostic and therapeutic aspects in brief. We discuss the results of our google survey to address the knowledge gaps. Diagnosis, principles and rationale of therapy and treatment of drug sensitive and drug resistant tuberculosis including the shorter regimen and regrouping of drugs are important considerations of our review.

1. Introduction

Tuberculosis (TB) management guidelines have been published by the International Union against Tuberculosis and Lung Diseases (IUTALD), then the World Health Organisation (WHO) and the Revised National Tuberculosis Control Program (RNTCP).[1–9] The implementation and practice as per guidelines was never much highlighted upon until the global threat of drug resistant tuberculosis (DR-TB) which boosted the process. Revisions or updates were majorly available from time to time but more so in the last few years. The technical and operational guidelines (TOG) for TB control in India were updated in 2016.[8] The WHO also released its comprehensive version of guidelines for drug susceptible tuberculosis (DS-TB) in 2017.[6] The WHO published the exhaustive DR-TB management guidelines in 2011.[10] With newer clinical trial data available they issued an addendum in 2016[11] and 2018.[12] They also incorporated analysis from individual patient data reported through the literature. The RNTCP revised its guidelines on programmatic management of drug resistant tuberculosis in 2017.[9] Subsequently in 2019, the WHO published its consolidated guidelines for DR-TB.[7]This pace of publication and knowledge gaps in practice are updated with activities like continued medical education, seminars and conferences. The accurate methods to understand the knowledge gaps have never been established in any form of education system including the medical education. With advent of the computer technology; google and applications connecting like-minded/student/working/professional people on the web have been used frequently in the non-medical curriculum. We used the google survey to study these gaps amongst the

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pulmonologists and subsequently review TB in 2019 focusing on the gaps in the survey.

2. Methodology

Google survey form on Tuberculosis in 2019 (Appendix 1) was made by the coordinating team and reviewed by the chief coordinator. It consisted of 15 questions targeting updates and basics of TB in 2019. They were multiple choice questions with three or four available responses but one correct answer. The final sequence of questions and the order of responses for each question was randomly assigned by the computer to avoid investigator bias. The google survey form was circulated to the target population consisting of chest physicians in western India. The email address was recorded for checking duplicate responses. The forms were circulated thorough Email and WhatsApp to three groups of chest specialists consisting of 500 individuals. One hundred and twenty five responses were obtained in the first week. After this the software was configured to stop accepting responses. Four duplicate responses were excluded. Thus, total 121 responses were obtained. Table 1 gives the summary of the answers obtained question wise (correctly or incorrectly). Based on the responses, literature search was done to focus on the knowledge gaps. Pubmed, Cochrane and Embase databases search for "update", "Tuberculosis","2019" revealed 2866 searches of which 18 were relevant and included in this final review targeting survey questions.

3. Discussion

3.1. *Tuberculosis- where do we stand?*[1–9]

TB is a known ancient disease wherein advances have taken place in phases over centuries and decades. Post introduction of rifampicin and the nation-wide roll out the RNTCP, there were no major changes. However the last few years had major changes in the management aspects as introduced above. We need to remember that though there has been a paradigm shift in diagnostics and therapeutics, the principles and rationales governing management of TB still remain valid. Practising something new must not be without the back up of these sound basics. The newer guidelines recommended the much need emphasis on 1) Diagnosis of TB &universal drug susceptibility testing (UDST), 2) Individualized management approach and not just DST based approach, 3) Patient centric care in form of direct observation of therapy (DOT) and support in other medical and socio-economic aspects, 4) Decentralisation of DS-TB/DR-TB services on the laboratory (microbiology) services, therapy and drugs distribution end, 5) Changes in DS-TB therapy, 6) Changes in DR-TBtherapy (Shorter regimen, individualised longer treatment regimen).[7]

Table 1 – Summary of Answers obtained to the questions in the Google survey form "Tuberculosis in 2019".

Question	Correctly answered (%)	Incorrectly answered (%)
First	65.8	34.2
Second	98.3	1.7
Third	72.3	27.7
Forth	100	0
Fifth	72.5	27.5
Sixth	30.8	69.2
Seventh	75.6	24.4
Eighth	60.2	39.8
Ninth	49.2	51.8
Tenth	73.3	26.7
Eleventh	64.1	35.9
Twelfth	87.5	12.5
Thirteenth	48.3	51.7
Fourteenth	82.5	17.5
Fifteenth	45.4	54.6

3.2. *Diagnosis of TB*[5–7]

The guidelines made a much awaited move towards microbiological confirmation of the disease and emphasize on the same to end empiricism in TB except in rare case scenarios. The WHO stressed on the need for universal access to DST in all suspected cases. The gold standard still remains the AFB culture testing by the liquid mycobacterial growth indicator tube (MGIT). However, the newer WHO approved rapid diagnostics (WRD) like cartridge based nucleic acid amplification test (CBNAAT) and the line probe assay (LPA) are now integrated in the diagnostic algorithm. Genexpert (GXP) is the commercially available CBNAAT. Newer methods like pyrosequencing are under research considerations and 65% respondents were aware of the same (Survey Question 11). All reports must be always reviewed with clinico–radiological correlation. One is well aware of the conventional RNTCP diagnostic algorithm. However, a simplified integrated diagnostic approach incorporating the WRD is illustrated in Fig. 1. The most important aspect of diagnostics include appropriate sample collection in suspect cases. The survey emphasized that sputum collection was practiced by all respondents in PTB suspects however one third did not collect appropriate samples for microbiological testing in cervical lymphadenopathy (Survey Question 4,5). In all PTB suspects, counselling should be done to collect deeply expectorated sputum representative of a lower respiratory tract sample with atleast 1–5 ml in quantity and with mucoid or mucopurulent consistency and not contaminated with food particles. Sputum induction with nebulized 3% hypertonic saline could be done in difficult cases and has equal results compared to invasive tests like bronchoscopy. In cases of lymphadenopathy a surgical excision or ultrasound guided trukut fine needle biopsy is preferred over fine needle aspirates. The survey revealed huge knowledge gap in this aspect (Survey Question 6). Pus is also a preferred sample with good yield for spine and other extrapulmonary sites. Pleural biopsy either a closed needle one or medical thoracoscopy guided has a better yield than examination of only pleural fluids. The various phenotypic and genotypic tests is mentioned in Table 2. The WHO also encouraged universal access to drug susceptibility test as per the national programmatic logistics. The RNTCP has relentlessly tried and upgraded its infrastructure to make this goal achievable with the CBNAAT and AFB culture tests available in HIV-TB, extrapulmonary TB and pediatric TB and in all TB

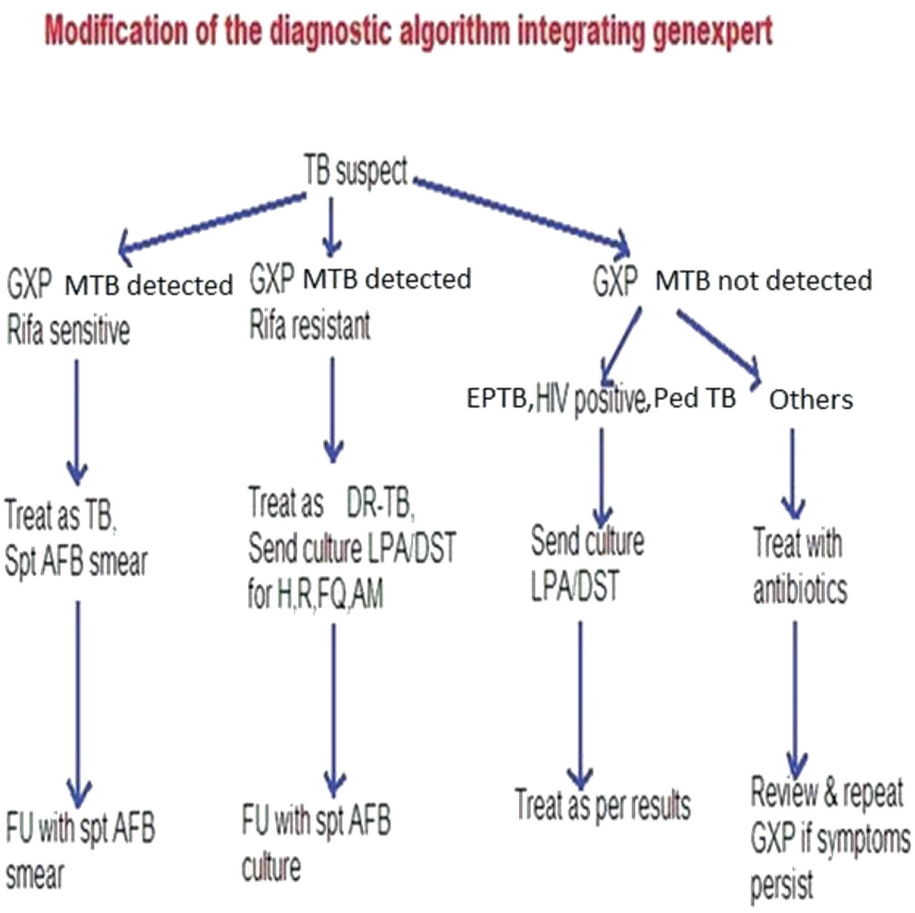

Fig. 1 – Modification of the diagnostic algorithm for tuberculosis (TB) using newer rapid diagnostics.

suspects in areas like Mumbai. Here also the survey revealed 27% respondents were unaware of the updates (Survey Question 3).

3.3. *Rationale of DS-TB therapy*[5,6]

Counseling about the disease and therapy is of utmost importance in any disease. TB therapy is a two phased therapy also known as short course chemotherapy (SCC). The intensive phase (IP) consists of the "quick kill" phase wherein 3 or more drugs to which the mycobacterium tuberculosis (MTB) is susceptible to are used. This phase is capable of killing the naturally occurring drug resistant mutants and hence prevents development of drug resistance. It consists of drugs Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E) administered as perkg body weight doses given for a duration of two months. The second phase is called the continuation phase which is capable of killing the "persisters" and prevent relapses. It consists of drugs H, R, E

Table 2 – Phenotypic and Genotypic tests in Tuberculosis.

Test	Principle	Turn around time	Pitfalls
Cartridge based nucleic acid amplification test	Genotypic	90 min	Detects only R resistance, False positivity with dead bacilli
Line probe assay	Genotypic	48 hrs	Can be applied only to a Smear or culture positive sample
Mycobacterial growth indicator tube	Phenotypic	10–15 days	Gold standard
Lowenstein Jensen culture	Phenotypic	24–42 days	Long turn around time

Table 3 – Drug dosages for drug susceptible tuberculosis.

Drugs	Adults mg/kg (Range)	Children mg/kg (Range)	Maximum permissible dose
Isoniazid	5 (4–6)	10 (7–15)	900
Rifampicin	10 (8–12)	15 (10–20)	900
Pyrazinamide	25 (20–30)	30 (30–40)	2000
Ethambutol	15 (12–18)	20 (15–25)	1600

administered as per kg body weight given for a duration of four months. This SCC is associated with best treatment outcomes and least relapse rates ever documented on any therapy. The addition of a single drug to a failing regimen also labelled as the "Addition syndrome" is a strict NO in management of TB. Physicians should never use second-line drugs empirically. The therapy should be given ALWAYS under direct observation or supervision. The supervision can be done by a medical, paramedical or lay person. This information was collected in Survey Question 7. The 99 DOTS system has been introduced under RNTCP which is a low cost monitoring system to ensure compliance to therapy. The medication envelopes are so designed that on dispensing the daily dose a toll free number is revealed. The patient has to call on the number on taking the drugs. The calls are free calls and not charged. Once the call is made the system registers in green that the dose is taken. If the call is not placed then the system generates an alert and the patient is reminded about the dose by message, call or an health visitor. The DS-TB therapy is safe and unchanged in presence of most comorbidities like DM, HIV. Renal diseases required dose adjustments according to the creatinine clearance. This aspect was correctly answered by most (Survey Question 12).

3.4. *DS-TB treatment*[8]

As per RNTCP 2016 guidelines the therapy for DS-TB consists of daily regimen with fixed dose combination initially consisting of 4 drugs H,R,Z,E for 2 months followed by 3 drugs H,R,E for 4 months as per weight bands for total duration of six months for all patients including (new and retreatment cases). The older nomenclature of category I, II and III are abolished. The survey revealed one third incorrect responses on this question (Survey Question 1). To be precise the recommended therapy for DS-TB consists of 8 weeks of IP-H,R,Z,E (4 drug FDC) and 16 weeks of CP-H,R,E (3 drug FDC). Streptomycin is no longer indicated. The survey revealed a very good percentage of correct responses for this question (Question 2). The drugs should be dispensed as FDC and split drugs should be avoided. Drugs are never given in divided doses. The drug dosages as per mg/kg body weight are mentioned in Table 3. The adult and pediatric weight bands are illustrated in Fig. 2. While there are no clear recommendations on checking serum rifampicin levels in DS-TB, the survey invited a variable response on this perspective (Survey Question 8).

3.5. *DR-TB*

Naturally occurring drug resistant AFB are known in literature since the availability of TB therapy. The occurrence of such resistance is rare and documented as 1 in 10^{7-8} forR, 1 in 10^{6-7} for H, 1 in 10^{5-7} for Z and 1 in 10^{4} for E. Rifampicin Resistance (RR) has been associated with poor treatment outcome to SCC & higher relapses. Thus the primary resistance occurring due to spontaneous mutation is rare and reported to be 2%. Secondary resistance occurring due to acquired causes like physician, patient related and logistics errors is reported to be 11–18%. Man-made errors cause selective growth of DR mutants which cause DR-TB.[13,14] Terminologies defining DR-TB have changed over the years as newer diagnostics are available. Current in use terminologies are Rifampicin resistant tuberculosis (RR-TB) is defined as TB caused by MTB resistant to R with or without resistance to other drugs. Multi-drug resistant tuberculosis (MDR-TB) is defined as TB caused by MTB resistant to H & R with or without resistance to E and/or Z. Pre-extensively drug resistant tuberculosis (Pre-XDR TB) is defined as TB caused by MTB resistant to atleast R with additional resistance to anyone fluoroquinolone (FQ) or anyone second-line injectable (SLI). Extensively drug resistant tuberculosis (XDR-TB) is defined as TB caused by MTB resistant to atleast R with additional resistance to anyone FQ and anyone SLI. Extremely drug resistant (XXDR-TB) is defined as XDR-TB with additional resistance (though unstandardized) to most of the available second-line drugs with poor clinical and microbiological response on the available DR-TB regimens.[15,16]

3.6. *Principles of DR-TB therapy*[5,7,9]

The basic principles of DR-TB management are derived from that of DS-TB. Hence, first and foremost being correct DIAGNOSIS with mandatory use of any of the DST methods. Seventy five percentage of respondents replied correctly on this (Survey Question 10). The diagnosis of DR-TB requires microbiological proof. Post diagnosis; counselling about the disease, therapy and enquiry into patient issues is suggested to provide a holistic patient centred approach. The direct observation of therapy is an important treatment aspect irrespective of the type of TB. The patient is treated with 4 or more drugs used for DR-TBtherapy to which the patient has never been exposed to in the past. Never add drugs to failing regimen. Minimally modify regimens for serious adverse events. Pretreatment evaluation suggested includes complete hemogram, fasting blood sugars, liver and renal function tests, urine routine microscopy, urine pregnancy test (in women of child bearing age group), psychiatric assessment, chest radiograph. Additional prerequisites like electrocardiogram, serum electrolytes, serum lipase, serum amylase, fundoscopy, audio metry evaluation have now been incorporated in the program with the newer drugs. Only 50% respondents

Weight bands

Adult DS-TB

Wt (Kg)	No. of tablets (FDC)	
	IP (H,R,Z,E) 75,150,400,275 mg	CP (H,R,E) 75,150,275 mg
25-34	2	2
35-49	3	3
50-64	4	4
65-75	5	5
>75	6	6

Ped DS-TB

Weight category	Number of tablets (dispersible FDCs)			Inj. Streptomycin
	Intensive phase		Continuation phase	
	HRZ	E	HRE	
	50/75/150	100	50/75/100	mg
4-7 kg	1	1	1	100
8-11 kg	2	2	2	150
12-15 kg	3	3	3	200
16-24 kg	4	4	4	300
25-29 kg	3+1A	3	3+1A	400
30-39 kg	2+2A	2	2+2A	500
A = Adult FDC (HRZE = 75/ 150/400/275; HRE = 75/150/275)				

Fig. 2 – Adult and Pediatric weight bands for drug sensitive tuberculosis (DS-TB).

seemed fully aware of these prerequisites (survey question 13, 15). A strict necessary referral for second-line LPA/DST should be done at baseline. The treatment regimens consist of the standardized shorter regimens versus the individualized longer treatment regimens. Follow up involves additional sputum AFB culture testing mandatory for patients on DR-TB therapy for pulmonary disease.

3.7. *Standardised shorter regimen in DR-TB*

The shorter regimen derives base from the studies of the Bangladesh Regimen.[17] Subsequently the regimen was studied under clinical trial conditions namely the Stream Stage I by the WHO. The results reported 80% treatment success.[18] This regimen now adopted by WHO and RNTCP consists of a standardised treatment consisting of 4–6 months of kanamycin (Km), moxifloxacin (Mfx), clofazimine (Cfz), ethionamide (Eto), Z, E, high dose H followed by 5 months of Mfx, Cfz, Z, E. Thus the total duration of therapy is 9–11 months (4–6 months of IP; 5 months of CP). The availability of the LPA first line & second line is a prerequisite and strict criteria for enrolment are recommended (Fig. 3). The dosages are given in Fig. 4.[7,9] Only half of the respondents answered the details on shorter regimen correctly (Survey Question 9).

Strict screening criteria for standardised shorter DR-TB regimens

Is any of the following present?

Preference by the clinician and patient for a longer MDR-TB regimen

Confirmed resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen (except isoniazid resistance)

Exposure to one or more 2nd line medicines in the shorter MDR-TB regimen for >1 month (unless susceptibility to these is confirmed)

Intolerance to medicines in the shorter regimen or risk of toxicity

Pregnancy

Disseminated, meningeal or central nervous system TB

Any extrapulmonary disease in PLHIV

One or more medicines in the shorter MDR-TB regimen not available

*If Yes – Patient is not a candidate for standardised shorter treatment regimen

Fig. 3 – Criteria for standardised shorter drug resistant tuberculosis regimen.

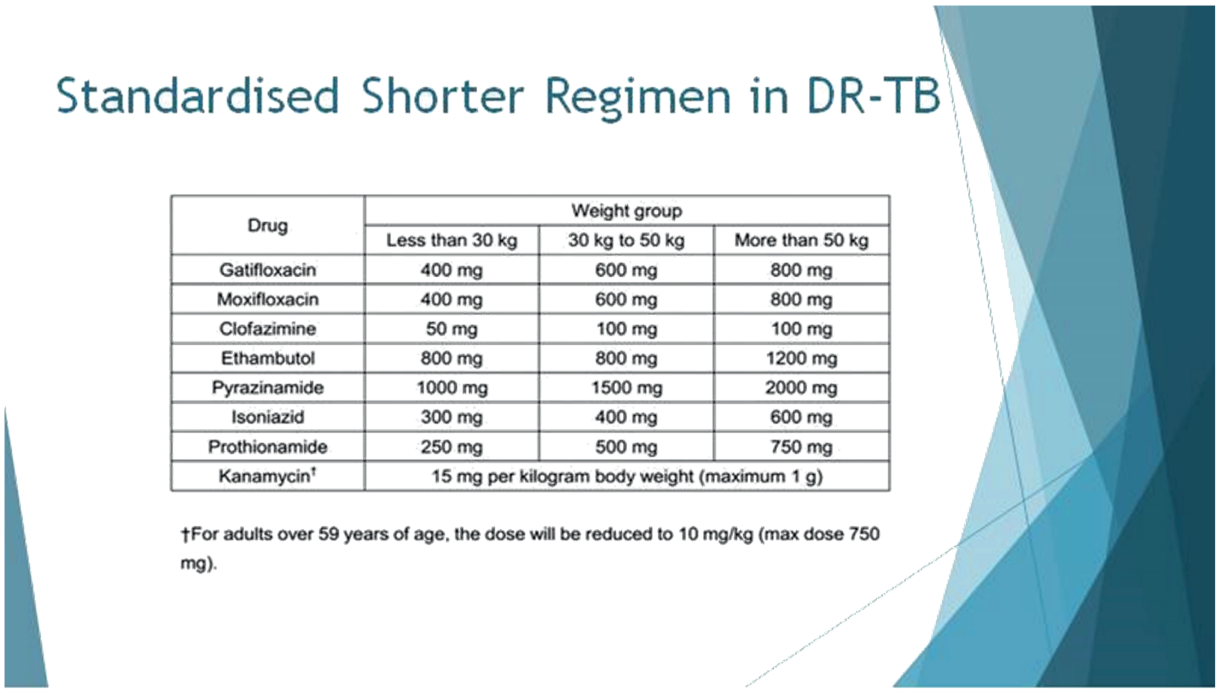

Fig. 4 – Weight bands for standardised shorter drug resistant tuberculosis regimen.

3.8. *Individualized longer treatment regimen*[7,9]

The individualised longer treatment regimens are formed applying the prior discussed principles of DR-TB therapy and using the drugs as per the regrouping of drugs for DR-TB (Fig. 5). All three Group A agents and at least one Group B agent should be included. At least 4 drugs likely to be effective and at least 3 drugs are included for the rest of treatment. If only one or two Group A are used, both Group B agents are to be included. If the regimen cannot be composed with Groups A and B alone, Group C agents are added to complete it. The duration of therapy is18–20 months. Km and Capreomycin (Cm) are no longer recommended for use in DR-TB regimens. With exclusion of injectables the therapy is no longer divided into intensive phase and continuation phase. Eto and Para-amino salicylic acid (PAS) had only showed effectiveness in regimens without bedaquiline (Bdq), linezolid (Lzd), Cfz, delamanid (Dlm). Bdq and Dlm are given only for six months

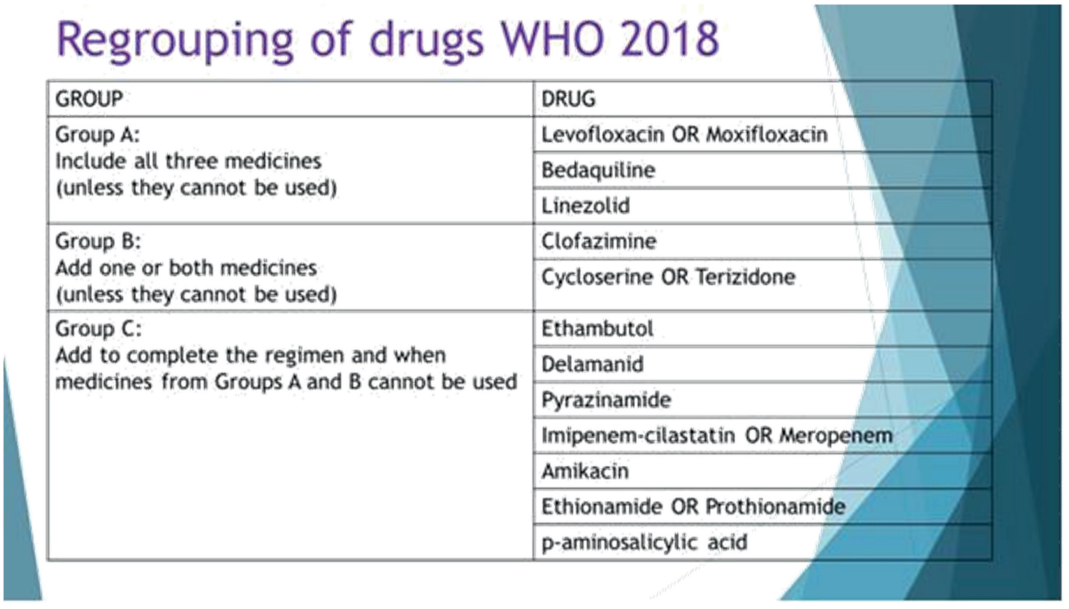

Fig. 5 – Regrouping of drugs for individualized longer treatment regimens in drug resistant tuberculosis.

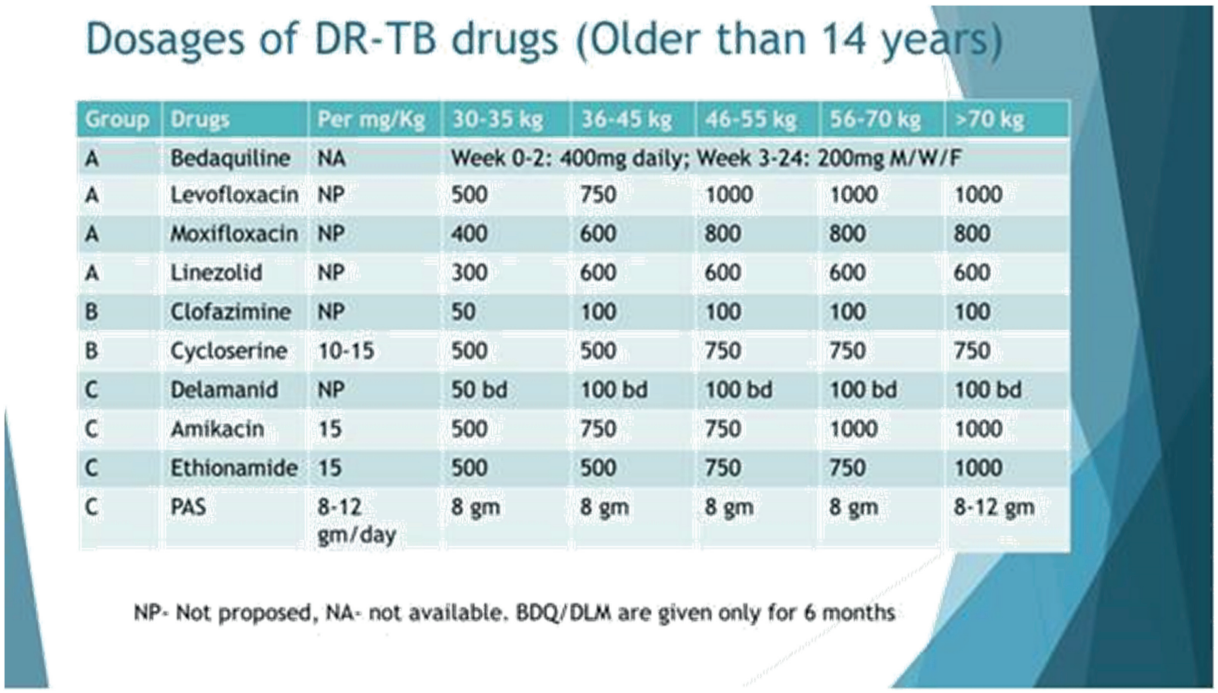

Fig. 6 – Drug Dosages for drug resistant tuberculosis (older than 14 years).

though are being tested for longer duration under trial conditions. Clarithromycin and Amoxycillin-clavulanic acid were not recommended as DR-TB drugs. The survey responders had good information on this (Survey Question 14). Figs. 6 and 7 give information on drugs dosages.

Thus we have complied a short review on tuberculosis in 2019 covering the important diagnostic and therapeutic aspects in brief. The complete management of TB is holistic and involves many more areas beyond the scope of any review article. The survey helped us gauge the knowledge gaps and

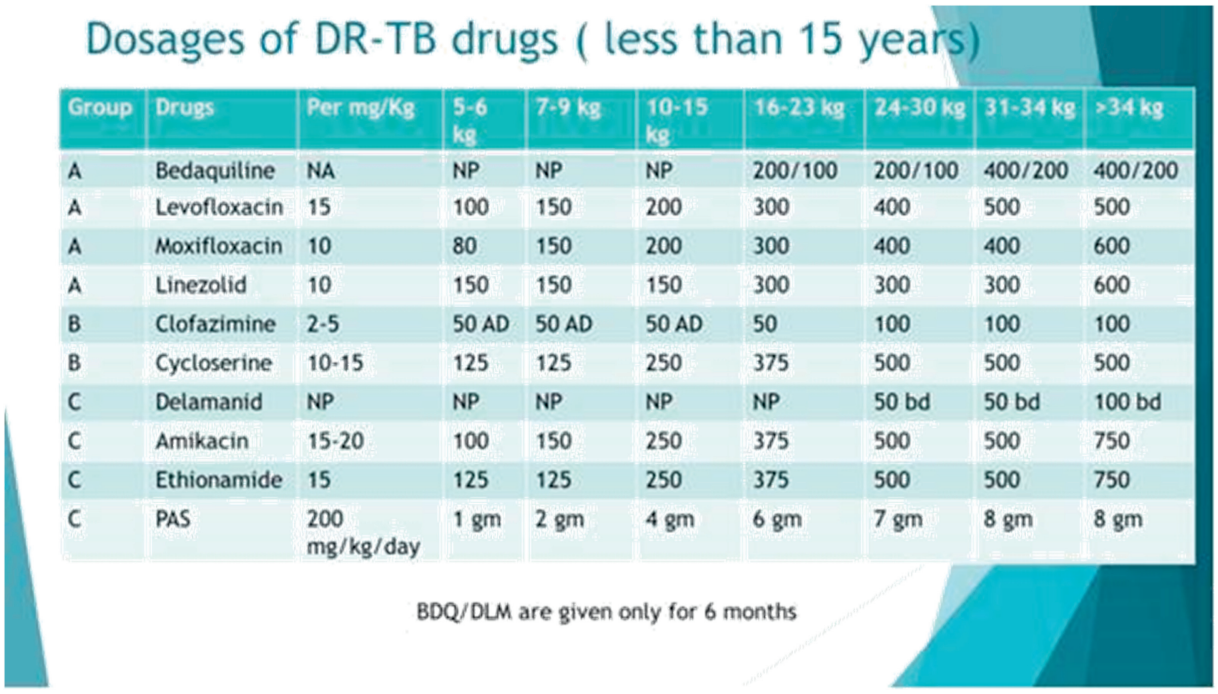

Fig. 7 – Drug Dosages for drug resistant tuberculosis (less than 15 years).

stress on important aspects of TB care in 2019 i.e. diagnostics with microbiological correlation and therapeutics considerations.

Conflicts of interest

The authors have none to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijtb.2019.08.013.

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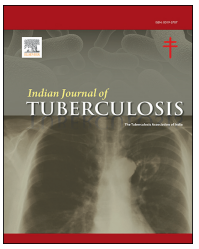

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Rifampicin and isoniazid behave as non-creatinine chromogens and interfere with Jaffe's reaction: A phenomenon with the potential to give a false-positive result in creatinine estimation

Keywords:
Jaffe's reaction
Creatinine
Tuberculosis
Anti-tubercular drugs
Spectroscopy

ABSTRACT

Tuberculosis is a health concern worldwide. The anti-tubercular drugs (particularly rifampicin) used for its management offers side effects like acute kidney injury. Creatinine, which is recognised as an important biomarker for the renal function, is commonly estimated with Jaffe's reaction (alkaline picrate reaction). However, interference of Jaffe's reaction with non-creatinine chromogens has been reported. In this context, we have checked the possibility of interference by Rifampicin and Isoniazid at therapeutic concentration with the Jaffe's reaction. Through in-silico study, we have studied the reaction prediction of picric acid with other chemicals/reactant (i.e. Rifampicin, Isoniazid and non-creatinine chromogens) in terms of confidence value. It is observed that the confidence value of reaction prediction between picric acid and INH and Rifampicin is much more than the same of pyruvic acid (non-creatinine chromogen). Further, we have checked the absorbance value of Jaffe's reaction mixture in aqueous media in the presence of both the drugs at 520nm. It is observed that the absorbance of alkaline picric acid increases with an increase in drug concentration. However, the increasing trend of absorbance is much more in the case of rifampicin compared to INH. It appears from our result rifampicin, and isoniazid has the potential to behave as non-creatinine chromogen and can give false positive creatinine results in Jaffe's reaction. Thus, it can cause misdiagnosis in patients consuming these drugs. We recommend study in the biological matrix for further validation of the result.

1. Introduction

Tuberculosis is endemic throughout the developing humanity, and currently, anti-tubercular medications are recommended for management of tuberculosis. Consumption of anti-tubercular drugs is at the cost of its side effects.[1] Anti-tubercular drugs apart from streptomycin are focussed to be hepatotoxic agents. However, Acute Kidney Injury (AKI) is common in patients on antitubercular medication. Rifampicin requires a particular mention in this regard as AKI is more common in patients consuming rifampicin.[2]

Serum and urine creatinine for calculation of Glomerular Filtration Rate is universally recognised as a biomarker of renal failure.[3] Creatinine is popularly estimated by alkaline picrate reaction (Jaffe's Reaction). Here, the colour is developed by reaction of creatinine with picric acid at alkaline pH.[4] This principle of estimation has been automated and popular for creatinine estimation in clinical biochemistry laboratories. The alkaline picrate reaction is interfered by non-creatinine chromogens, which produces a false-positive result.[5] Recently we have shown that streptomycin at high doses can act as a non-creatinine chromogen.[6]

Currently, it is not known that rifampicin and Isoniazid (INH) acts as a non-creatinine chromogen or not. In case rifampicin and INH interfere with alkaline picrate reaction in therapeutic concentration (0.2–20μm/ml in case of Rifampicin and 0.1–10μg/ml in case of INH) the drug itself will be a source of falsely positive creatinine result.[7] In that case, it will produce a misleading diagnosis.

Therefore, in this study, we have checked the possibility of interference of Rifampicin and INH at therapeutic concentration with the alkaline picrate reaction.

2. Materials and methods

2.1. *In-silico study*

The IBN RXN for chemistry web service available freely through www at https://rxn.res.ibm.com/is used for predicting the in-silico chemical reactions.

The structure of picric acid, creatinine, Rifampicin, Isoniazid, and non-creatinine chromogens (i.e. Acetone, Pyruvic acid, Acetoacetic acid, Vitamin C and Glucose) were added using the smiles string editor option.[8] The structure is then saved to templates. The "run prediction" tool is used to predict chemical reactions. The feasibility of the chemical reactions is estimated in terms of "Confidence" value.

2.2. *In vitro study*

Chemicals: Picric acid from BDH, Creatinine from S D Fine Chemical Ltd, Rifampicin form Cadila Pharmaceuticals Ltd, INH and NaOH from Himedia were used.

2.3. *Preparation of solutions*

1. Picric acid (0.04M) was prepared by dissolving 0.0910g of picric acid in 10ml of DW.
2. Creatinine (0.7mg/ml) was prepared by dissolving 0.0070g of creatinine in 10ml of DW.
3. NaOH (0.75M) was prepared by dissolving 0.3g of NaOH in 10ml of DW
4. Rifampicin (2.18mM) prepared by dissolving 1.8mg in 1ml of DW
5. INH (6.56mM) prepared by dissolving 0.9mg in 1ml of DW

The effect of different concentration of Rifampicin (0, 4, 8, 12, 16, 20, 40μg/ml) and INH (0, 2, 4, 6, 8, 10, 20 μg/ml) in constant creatinine concentration (20μl of 0.7mg/ml) in alkaline picrate reaction was studied through spectral study. Similarly, the effect of different concentration of creatinine (0, 10, 20, 30, 40, 50, 100μl of 0.7mg/ml) in constant drug concentration (20μg/ml in case of rifampicin and 10μg/ml in case of INH) was studied. The Spectral study was performed at wavelength 520nm using TECAN Infinite 200 Pro M PLEX multimode reader by setting the instrument in default mode.

Statistical analysis: All values of absorbance obtained are represented as mean ± SD (n = 6). The unpaired t-test is used to compares the values obtained. P-value $\leq$0.05 is considered to be significant.

3. Results

3.1. *In silico study*

The reaction prediction value of picric acid with other reactant/chemicals in term of confidence value using IBN RXN is given in Fig. S1. It is observed that the confidence value of reaction prediction between picric acid and INH and Rifampicin is significantly more (p-value <0.05) than the same of pyruvic acid. It is well known that pyruvic acid is a non-creatinine chromogen which interferes with alkaline picrate reaction. As the confidence value of rifampicin and isoniazid is high than pyruvic acid, there is a high chance that it interacts with picric acid and interferes in alkaline picrate reaction and behave as the non-creatinine chromogen.

3.2. *In vitro study*

Through absorbance recording at 520nm, it is observed that the absorbance value of the reaction mixture increases significantly ($p < 0.05$) on increasing the concentration of rifampicin (0,4, 8, 12, 16, 20, 40μg/ml) in the presence of constant amount of creatinine (20μl of 0.7mg/ml) in alkaline picrate reaction (Fig. 1a). However, in the case of INH, the absorbance values change with the increase in INH concentration (0, 2, 4, 6, 8, 10, 20μg/ml) with a slightly increasing trend. All values do not increase with the increase of the drug. Sometimes there is decrease even (Fig. 1b).

In addition, the effect of increasing concentration of creatinine (0, 10, 20, 30, 40, 50, 100μl of 0.7mg/ml) with constant drug concentration (10μg/ml in case of INH and 20μg/ml in case of rifampicin) in alkaline picrate reaction shows a linear trend (Fig. 1c and d).

Both INH and Rifampicin are found to be readily soluble in distilled water as expected. However, INH produced a clear solution, but rifampicin produced an orange colour solution (Fig. 1e and f).

4. Discussion

The results demonstrate that as expected from the in-silico results (Fig. SI), the tested antitubercular drugs increase the absorbance of a fixed concentration of picric acid at alkaline pH. The increasing trend of absorbance of alkaline picric acid after drug addition is much more in case of rifampicin compared to INH. So rifampicin has the potential to act as a more significant non-creatinine chromogen. We feel that both the drugs should be considered for testing for interference producing in Jaffe's reaction in the biological matrix (serum, urine, etc.).

The results raise the concern that rifampicin and INH can behave as a non-creatinine chromogen and so can produce a false-positive result in creatinine estimation by Jaffe's method. Our experiments validate the above concern In aqueous media in the therapeutic concentration of the tested antitubercular drugs. So the concern raised by the primary findings has the potential to be the reason for misdiagnosis of renal status in patients receiving these drugs. Since tuberculosis is a common condition and many patients are receiving these drugs, the findings require urgent confirmation in the biological matrix and if kidney status is required to be checked in patients consuming these drugs creatinine estimation methods other than Jaffe's method may be used.

The colour of the rifampicin solution is orange as expected. Apart from rifampicin interaction with picric acid, it may be an

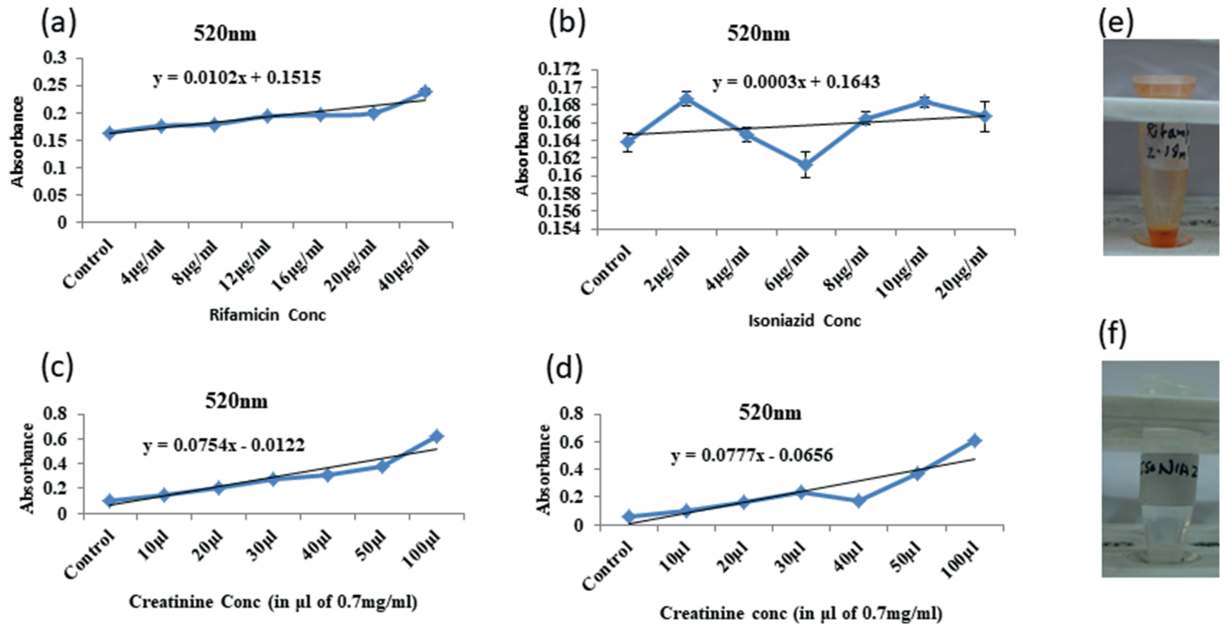

Fig. 1 – Shows the effect of different concentration of (a) Rifampicin, (b) Isoniazid (in DW) on the absorbance value by keeping the concentration of creatinine constant (20μl of 0.7mg/ml) in Jaffe's reaction. The effect of varying concentration of creatinine (in DW) on the absorbance value by keeping the concentration of drug constant, i.e., (c)Rifampicin (20μg/ml), (d) Isoniazid (10μg/ml) in Jaffe's reaction. (e) Rifampicin solution (orange in colour), and (f) Isoniazid solution (clear).

independent cause of interference in Jaffe's reaction in the presence of rifampicin. Therefore, the interaction of these drugs with picric acid is to be studied to be sure of these aspects.

We conclude by saying that it appears from our result INH and rifampicin has the potential to behave as non-creatinine chromogen when added with picric acid. This has the chance to produce false-positive creatinine results. That, in turn, will produce misdiagnosis in patients consuming these drugs. Particularly screening of AKI, which is a known side effect of rifampicin and other antitubercular drugs may be affected, is creatinine is estimated employing Jaffe's Reaction. So clinical validation of our observation is to be done on an urgent basis.

Conflicts of interest

The authors have none to declare.

Authors contribution

DK, RB, and DB developed the concept and obtained the funding. The experimental works are entirely done by DK and Supervised by DB. The In-silico work is done by SS and supervised by RB. All the authors have repeated the experiment and approved the final version of the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijtb.2019.08.012.

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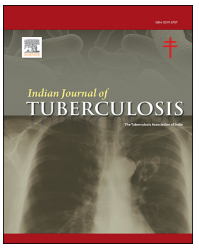

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Tuberculosis of the gallbladder-another one of its many faces

Keywords:
Gallbladder tuberculosis
Mimicker of carcinoma
Computed tomography

ABSTRACT

Abdominal tuberculosis is not uncommon in developing countries which usually presents as involvement of ileo-caecal junction. Involvement of gall bladder by tuberculosis is rare and thus, imaging diagnosis is unlikely. The diagnosis is confirmed only on histopathology. We present a case of a middle-aged Indian female with tuberculosis of gall bladder who was diagnosed after image guided biopsy and was managed with anti-tubercular treatment.

1. Introduction

Tuberculosis affecting the abdominal organs is reported to have an incidence of 12% in developing nations.[1] Involvement of gall bladder by tuberculosis is rare and was first reported in 1870 by Gaucher.[2] A coexistent high prevalence of gall bladder carcinoma poses a diagnostic challenge.

2. Case presentation

A 38-year-old Indian female belonging to a low socio-economic status presented with pain in the right hypochondrium, low grade fever without chills and weight loss for the past 2 months. There was no past history of tuberculosis, jaundice or hepatitis. Her routine laboratory investigations and chest radiograph were unremarkable except for raised ESR (32mm/h) and low haemoglobin (9g/dL). She underwent an ultrasound examination of the abdomen which revealed thickened gall bladder wall with a mass lesion infiltrating into the liver from the gall bladder fossa. There was no evidence of any gall bladder calculi. There was associated splenomegaly and mild ascites. With a high suspicion of gall bladder malignancy, a CECT of abdomen was advised. The CT exam revealed nodular thickening in the gall bladder fossa (arrowhead, Figs. 1–3) with poor fat planes with the adjacent liver. Mild ascites was also noted with gross splenomegaly (Fig. 3). Multiple enlarged, discrete lymph-nodes, few of them with necrotic centre were noted in pre, para-aortic and peri-portal region were also seen (Figs. 4 and 5). The bowel loops were unremarkable with normal ileo-caecal junction. Overall, on imaging, a gall bladder fossa mass with possibility of liver invasion was kept as the diagnosis. The patient then underwent ultrasound guided biopsy of the lesion which surprisingly turned out to be a granulomatous lesion with caseating necrosis and giant cells, suggesting a tubercular aetiology.

3. Discussion

As low as 1% cases of abdominal TB present with gall bladder involvement.[3] Usually these cases present with cholelithiasis and secondary cholecystitis. It has been hypothesised that tubercular bacilli form a nidus on the calculi.[4] Occurring more commonly in older women[5] with our case involving a middle-aged female. There are no specific imaging features. However, nodular deposits, gall bladder wall thickening and gall bladder mass have been reported in cases with TB of gall bladder.[6] Pre-operative diagnosis is unlikely and final diagnosis relies on histological analysis. Concomitant high incidence of gall bladder malignancy and lack of any pathognomonic imaging findings makes a definitive imaging diagnosis unlikely.[7] When diagnosed pre-operatively, the management comprises of anti-tubercular treatment with surgery being indicated only in symptomatic patients.

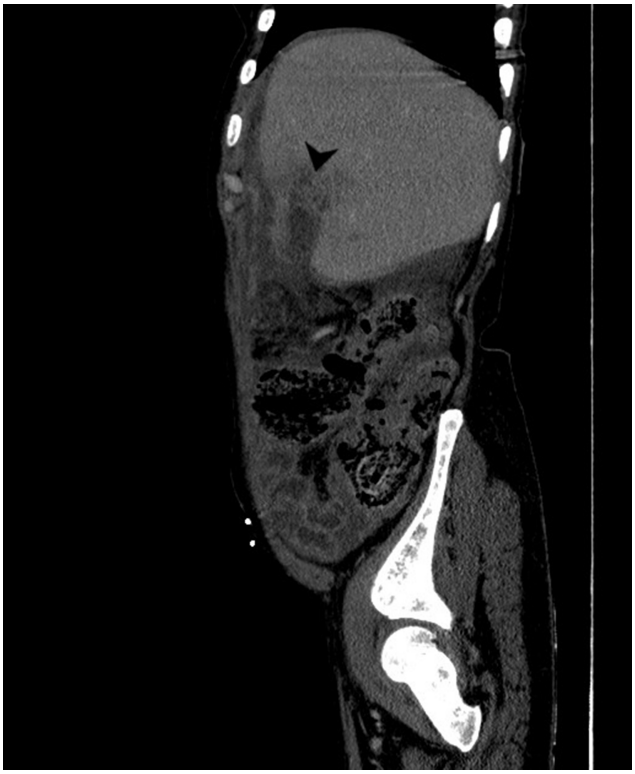

Fig. 1 – Sagittal non-enhanced CT shows an ill-defined mass lesion in the gall bladder fossa with fat planes not clear with the adjacent liver parenchyma (arrowhead).

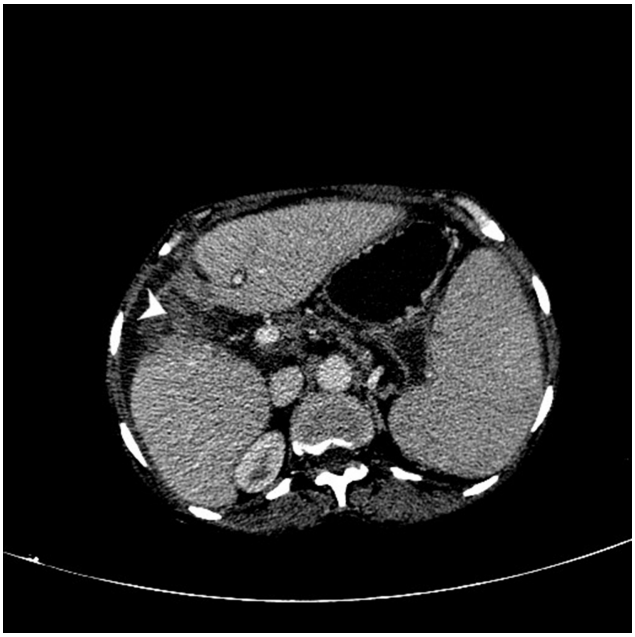

Fig. 2 – Axial contrast enhanced CT at the level of the gall bladder fossa shows a conglomerate nodular enhancing deposit (arrowhead).

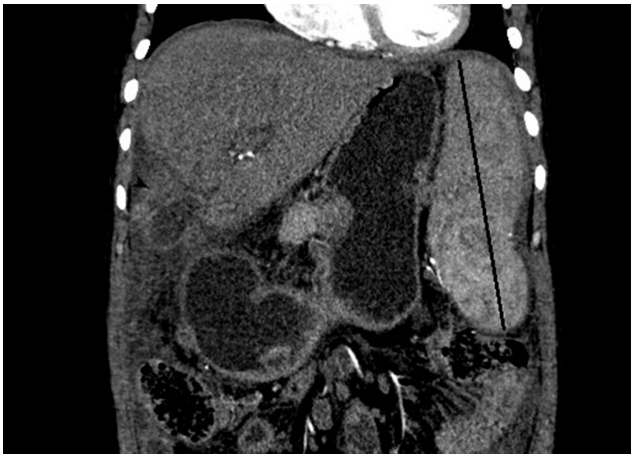

Fig. 3 – Coronal contrast enhanced CT shows a conglomerate nodular mass (arrowhead) around the enhancing gall bladder. There is associated splenomegaly with mild ascites.

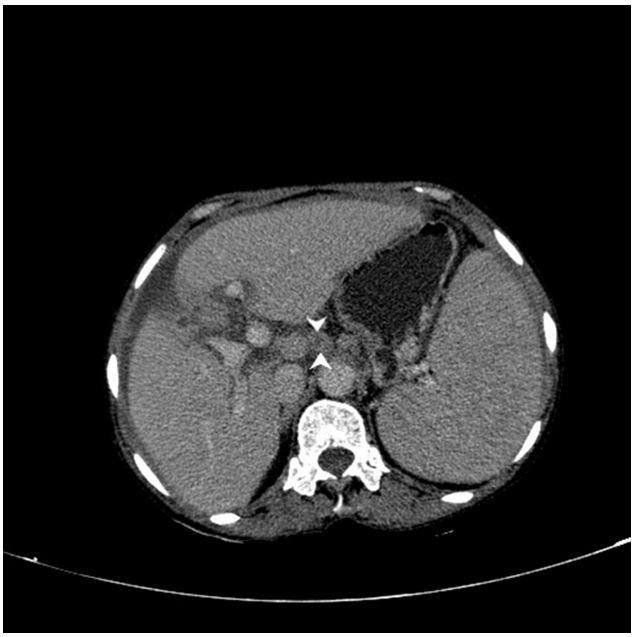

Fig. 4 – Axial contrast enhanced CT at the level of porta shows a pre-aortic lymph-node with central necrotic areas (Arrowheads). Another smaller node is seen adjacent to it.

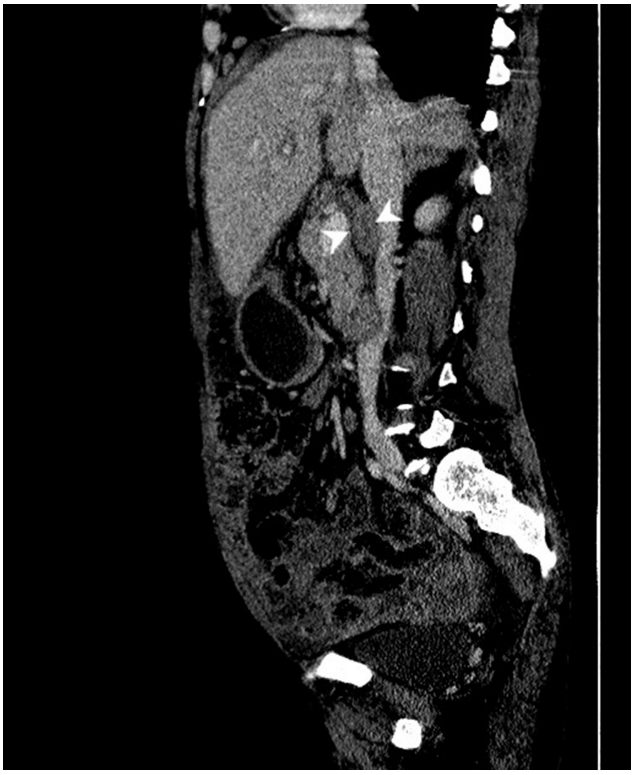

Fig. 5 – Sagittal contrast enhanced CT shows the same pre-aortic lymph-node (arrowhead).

4. Conclusion

A high index of suspicion in the appropriate clinical setting is necessary to identify this rare presentation of tuberculosis. Histological analysis is necessary in order to confirm the diagnosis and institute appropriate management. Image guided biopsy is a proficient method to establish the diagnosis.

Conflicts of interest

The authors have none to declare.

Author contributions

Author AA and RK conceived the idea of the manuscript. Authors AA and A prepared the first draft. Author RK and MB were the primary consultants. Author AA and A undertook the literature review, medical management of the patient and was the primary physician.

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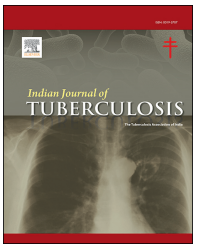

Correspondence

Anti-tuberculous drug induced liver injury – Do we need to rethink?

Keywords:
Anti-tuberculous therapy
Hepatitis
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Dear sir

The latest World Health Organization report (2018) includes India among the thirty tuberculosis (TB) high-burden countries, contributing to 22% of the annual global TB burden with 10% of children (<14years) being affected.[1] As the world has now adopted the global strategy to achieve "Zero death by TB", the Revised National Tuberculosis Control Program (RNTCP) initiated by the Government of India has been updated to achieve a reduction in the burden of disease in order to be at par with global goals. Recent changes in RNTCP include change in the dose schedule from thrice weekly to daily for all types of tuberculosis[2] and an increase in the average dosing of first line anti-tuberculosis treatment (ATT) drugs.[3]

Being a tertiary-care centre catering to many complicated TB cases, we have noticed an upsurge in the incidence of anti-tuberculous drug induced liver injury (ATDLI) in the recent years. Previous studies have also concluded that higher drug doses of isoniazid and pyrazinamide have been associated with an increased risk of ATDLI.[4] Diagnosis of the ATDLI warrants withholding of the hepatotoxic agents of the first-line treatment regimen (Pyrazinamide, Isoniazid and Rifampicin) with supportive management and close monitoring of liver functions. Reintroduction of the ATT is then gradual, once the liver function tests are within the acceptable range. This process not only takes at least 9 days causing delay in potential discharge (or multiple hospital visits if treatment is on outpatient basis) but also causes interruption in ideal treatment with first-line drugs. Secondly, we have also observed recurrence of ATDLI for the second time after re-initiation of first-line treatment in some children following which these drugs cannot be offered to them again. Thirdly, some patients may require concurrent administration of other hepatotoxic drugs for other indications which, with ATT, may synergistically contribute to the hepatotoxicity (e.g. CNS TB requiring anticonvulsants). Possible reasons for this upsurge in ATDLI include increased drug doses, genetic polymorphisms, etc. Future research in this regard is the need of the hour.

Statistical analysis

Not applicable.

Conflicts of interest

The authors have none to declared.

Ethical statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Authors' contribution

JP, PM: literature review, and initial draft manuscript preparation;

LS, SV: Critical review of manuscript for important intellectual content.

All authors approved the final version for publication.

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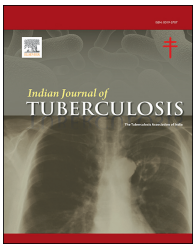

Correspondence

Making survival in TB defaulter patient: A key challenge

Recently, one study demonstrated the survival analysis of defaulter TB patients. For the survival analysis, the outcome of interest was treatment defaulter and the purpose of their analysis, only the times for patients who were defaulted were taken as event.[1] Tuberculosis (TB) is an infectious disease which continues to be the leading cause of death. According to the Global TB Report 2017, released by the WHO, India has topped list of seven countries accounting for 64% of over 10 million new TB cases worldwide in 2016. An estimated 1.7 million people died from TB in 2016.[2] Substantial progress has been made in reducing tuberculosis incidence over the past two decades. However, Tuberculosis (TB) continues to be one of the most devastating and widespread infections in the world, if left untreated, each person with active TB disease will infect on an average between 10 and 15 people every year. Defaulters from treatment of pulmonary tuberculosis (PTB) convey a significant transmission risk that is particularly dangerous during increasing prevalence of MDR-TB (Multi Drug Resistance-TB) and TB/HIV. TB/Diabetes co-infection. Various risk factors and timing of default from treatment for non-MDR-TB and default has been associated with increased mortality and amplification of drug resistance and may contribute to the high MDR-TB[3] Of particular relevance in India, default and sub-optimal adherence may increase the probability of acquired drug resistance of TB cases specifically returning after treatment default (a subset of all those that have previously received treatment) in India (last one decade), 64% had MDR-TB.[7] Key barrier to survival is treatment default, defined as treatment interruption for at least two consecutive months. Default can undermine effective TB control because patients with sustained non-adherence to treatment may remain infectious[3] and suffer an increased risk of TB recurrence and TB-related mortality. Given the importance of reducing treatment default for preventing acquired resistance and minimizing the prevalence of untreated drug-resistant TB, we sought to identify risk factors and temporal patterns of treatment default among TB cases without MDR-TB in one study carried out by us in Gwalior city of Madhya Pradesh.[4] We identify individual-level risk factors for default among non-MDR-TB cases. We also examine the time at which individuals defaulted to permit better insight into potential causes of treatment default. Identifying host- and time-related risks of default may facilitate the deployment of targeted interventions. We calculated the percentage of cases that defaulted on treatment overall and by year to year among cases with confirmed outcomes or still on <1 year of treatment on 16 October 2018. We used a least squares regression to detect linear trends in the fraction of cases that defaulted by year weighting each data point by the number of TB cases included. We also investigated the timing of default separately for new and previously treated cases, including only those cases that defaulted within the first year of treatment. We excluded observations that were missing diagnosis or treatment result date and observations were recorded treatment result date preceded diagnosis date. Of non-MDR-TB cases notified between 2016 and 2018, 14.8% defaulted on treatment (13.4% of new cases and 23.6% of previously treated cases). Among the categories of previously treated cases, those returning for treatment after a previous default had the highest default risk (44.6%) and this was found similar to study carried in Maldove.[5] There was no peculiar trend in the percentage of patients defaulting on treatment 2016–2018. The Median survival time was 11.4 years in patients who completed treatment, while 6.9 years was in those who were defaulter. There were substantial differences in default risk between different socio demographic variables among new cases and previously treated cases. In our study, 89.60% of defaulters were documented during continuation phase. This may be due to less vigilant follow-up of patients during continuation phase as compared to intensive phase. This is similar the findings of Ajagbe et al [6] which had shown 70% patients interrupted treatment during continuation phase. In the age group of above 60 years the probability of survival was 42.6% (SE = 0.54) in comparison to the cumulative survival rate was 63.8% (SE = 1.4), it should be noted that the highest mortality rate (13.5%) was found in the older (>60 years) age group. Survival group has the significant lower mean age 42.6 ± 18.2 in comparison to death group age 64.8 ± 18.3. Majority of survival patients were found in females (78.5% vs 69.8%) and among the age

group of 15–35 & 35–55 years. Survival were also found more in the group not associated with history of HIV+, diabetes, kidney disease, cancer, smoking. It should be noted; the risk value has been constant value overtime and has not depended on time. The findings of the exponential regression multivariate test showed that the survival rate was 60% more in patients with negative smear. Key strengths of survival study in TB treatment defaults is that is provided valid evidence and documentations for long term survival of patients with history of TB defaulters. Our little expression on survival in TB treatment defaulter showed that not successful treatment of PTB (Pulmonary Tuberculosis) has an adverse effect on the patients' survival and caused a decrease in their survival rate in long-term.

1. Conclusion

Treatment default also poses a public health threat, because individuals who do not complete therapy are more likely to remain infectious. The consequences of default from drug-resistant TB treatment may be particularly grave, because effective therapy for patients with drug-resistant. TB relies on the remaining drugs to which the strain has in vitro susceptibility. Thus, treatment default may lead to the transmission of TB that is more difficult to cure with existing drugs. The implementation of interventions designed to facilitate treatment completion for vulnerable groups is crucial to the success of programs that provide long-term therapies.

Furthermore, the high mortality rate associated with treatment default and the large proportion of patients who had positive culture results at the time of treatment default emphasize the critical role for prevention of treatment default may play in minimizing TB-related mortality and reducing the ongoing transmission of M. Tuberculosis infection.[7] Given the predictors of survival in defaulters, it has been suggested that an appropriate strategy be adopted for active prognosis in individuals with degree of default and also their immediate treatment be conducted. Also, in order to make the treatment efficient in patient with positive smear PTB and in order to reduce the recurrence and cutting off the treatment the directly observed short course treatment should be strengthened.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijtb.2019.10.005.

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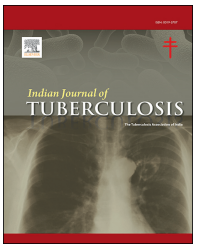

Correspondence

Tuberculosis and novel Wuhan coronavirus infection: Pathological interrelationship

Dear Editor,

New emerging infectious disease is usually an important global public health consideration. In December 2019, a new viral disease was reported from China. The infection is due to novel coronavirus. The infection can cause the febrile illness and severe respiratory problem.[1] At present, this disease has already been imported to many countries such as Thailand, Japan and South Korea.[2] As a new disease, the knowledge on this infection is limited. In developing countries, there are usually many common endemic diseases. There is a chance that there might be a concurrence between new disease and endemic disease. Regarding respiratory infectious disease, tuberculosis is common in several countries. The concurrence between tuberculosis and the novel Wuhan coronavirus infection is an interesting issue in clinical mycobacteriology. Based on the available data (21 January 2020), there are at least 221 cases of novel Wuhan coronavirus infection. Of these cases, there is a case with tuberculosis coinfection giving the rate equal to 0.45%. There are 6 death cases including to the case with tuberculosis coinfection. Based on this data, it might imply that tuberculosis might be associated with mortality risk in Wuhan coronavirus infection (death rates among the patients without tuberculosis versus with tuberculosis are 2.27% versus 100%). The left question is whether there is any interrelationship on pathogenesis of tuberculosis and Wuhan coronavirus infection. Further studies on this specific issue is interesting.

Conflicts of interest

The authors have none to declare.

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Case report

Lessons learnt from an old foe

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CSF-cerbrospinal fluid

ABSTRACT

Neurotuberculosis usually responds well to standard antitubercular therapy. Some; patients have prolonged course A 11 year old boy diagnosed TBM, an immunocompetent patient, had an unusual course of illness in the form of prolonged fever, persistent hyponatremia and CSF; pleocytosis despite adequate treatment. Clinical course in the management of TBM can be; protracted with complications despite adequate therapy.

1. Introduction

The most lethal clinical presentation of tubercular infection is tubercular meningitis (TBM). It has a prolonged course requiring treatment for at least a year. Complications of TBM are known to develop during the course of the illness as well as after initiating treatment. These complications are the important cause of mortality and morbidity in TBM. Early recognition and prompt management of these complications reduces the brain injury as well as improves the chances of good outcome.[1]

2. Case report

A 11 year old previously well boy presented with fever, headache, and vomiting of 3 weeks duration. He had generalised seizures 3 days prior to admission. He gave a h/o weight loss. He also complained of diplopia and photophobia. There was no history of contact with tuberculosis. O/e he appeared sick. pulse −104 beats per minute, RR- 28, BP- 110/70 mm of Hg. BCG scar +, weight − 20kgs, Height- 130cms, BMI-11.3. He was irritable and had a GCS of 12/15 with irrelevant speech. Cranial nerve examination revealed Right Lateral rectus palsy with other cranial nerves being normal. He had meningeal signs in the form of neck stiffness.

Motor and sensory system examination was normal and there were no cerebellar signs. Other systemic examination was within normal limits.

Complete blood count was normal. Hyponatremia with normal potassium levels was noted. HIV Elisa − negative. Mantoux test was (10mm) positive. CSF analysis done outside showed lymphocytic pleocytosis, high protein and low sugar (Table 1). Neuroimaging done following admission showed mild communicating hydrocephalus. There were no basal exudates or infarcts. A diagnosis of tubercular meningitis was made and ATT was started along with steroids. Considering

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Table 1 – CSF results.

CSF parameters	1st	2nd	3rd	4th
TC	145	450	450	nil
DC	2/98	15/85	80/20	
Protein	228	179	>500	311
Sugar	45	29	30	40
Gene expert		positive		

the possibility of partially treated pyogenic meningitis ceftriaxone was added.

Child continued to be in altered sensorium with persisting fever even after a week treatment with ATT. He also developed polyuria during his stay in hospital and had persistent hyponatremia. A repeat neuroimaging showed no worsening when compared with the previous images. CSF analysis was repeated in view of persistent fever, was positive for gene expert and was rifampicin sensitive. However, there was increase in cells (predominantly lymphocytic) in the CSF fluid when compared with the previous analysis. Hence antibiotics was changed to meropenem thinking of possible resistant pyogenic meningitis and ATT was continued.

The child was evaluated for polyuria. He was clinically dehydrated with low sodium levels Serum osmolality - 264 (278–298 mOsm/kg) was low, along with high urine sodium-105 and Urine osmolality –280 (300–900). Potassium levels were normal. Based on this, the possibility of cerebral salt wasting was considered and he was managed accordingly with fluids and added salt. However, due to persistent polyuria and symptomatic hyponatremia unresponsive to fluid and salt management alone, fludrocortisone was added following which sensorium improved. and urine output normalised.

Meanwhile, he was investigated for persistent fever. It was noted that serial blood counts showed progressive lymphopenia with normal peripheral smear. A repeat CSF analysis was considered since second CSF analysis showed an increase in the cell count. A neutrophilic predominance pleocytosis when compared with the previous CSF analysis (total CSF cell count – Normal) with hypoglycorrhachia was noted. Vancomycin was added, ATT and steroids were continued. In view of a prolonged course of illness and peripheral blood showing progressive lymphopenia and with acquired immunodeficiency being ruled out, flowcytometry was done which showed low CD4 53 (553–1300/cumm) and CD8 75 (330–920/cumm).

Fever subsided gradually after 4 weeks of ATT. Polyuria also resolved in 3 weeks and Serum sodium levels stabilised. Fludrocortisone was tapered and stopped subsequently A fourth CSF analysis done at 4th week of ATT treatment showed no cells with improving glucose. He was discharged on ATT. Flowcytometry repeated on follow up showed improving CD4 and CD8 count. He has completed antitubercular treatment and is currently asymptomatic with no neurological sequelae.

3. Discussion

Hyponatremia is one of the commonly occurring systemic complication seen in about 35–65% of patients with TBM.[2] The main causes of persistent hyponatremia in TBM are SIADH and CSW. Formerly SIADH was considered the probable mechanism of hyponatremia in TBM. However, in most cases of TBM, CSW is the main cause of hyponatremia.[3] CSW is diagnosed with the evidence of polyuria, depletion of intravascular volume and natriuresis despite hyponatremia. Fluid and water replacement is the cornerstone in treatment of CSW. Fludrocortisone in the dose of 0.1–1 mg/day in two divided doses is also used in management of CSW. Hypokalaemia, pulmonary oedema and hypertension are potential side effects of longterm use of fludrocortisone.[4] Hence it should be used when diagnosis of CSW is confirmed and management with fluid and salt replacement alone is difficult. CSW resolves once the underlying pathology improves.

CD4 and CD8 lymphocytes play an important role in protective response against tubercular infection. Studies have shown that CD 4 lymphocytopenia is more pronounced in disseminated/meningeal form of tuberculosis. CD4 and CD8 lymphocytes levels revert back to normal following treatment. One of the hypothesis to explain such low levels of CD4 and CD8 include containment of these cells in the affected organ rather than the circulation.[5,6]

Defervesce of fever following treatment along with clinical improvement are considered as response to treatment. Persistence of fever even after treatment in TBM, one must first ensure compliance with therapy. Other possibilities to consider in cases of prolonged fever in TBM included MDRTB, immunodeficiency, super added occult or co infections and lastly drug fever. In our patient all the above was ruled out. The factors affecting the duration of fever in tuberculosis are not very clear. The exact duration for fever to subside in tuberculosis following treatment is not known. Our child was afebrile after 4 weeks of ATT.[7]

Lymphocytic predominant pleocytosis, hypoglycorrhachia with high protein level are the usual CSF findings seen in TBM. Various studies on serial CSF changes in patients on treatment for TBM have highlight the following: (*i*) rate of normalisation of CSF is variable and slow (*ii*) Euglycorrhachia is achieved first, followed by normalisation of cells and then protein (*iii*) there are no studies on changes in the lymphocyte and PMN counts individually following treatment (*iv*) CSF parameters can initially worsen after ATT is started.[8]

This case highlights that TBM may have a prolonged course despite adequate treatment. CSF pleocytosis may worsen after starting ATT. Transient lymphopenia can occur with severe forms of tuberculosis; CSW is rare life-threatening complication of TBM which needs to be managed aggressively.

Contributors

All authors contributed equally in patient care and manuscript preparation.

Conflicts of interest

The authors have none to declare.

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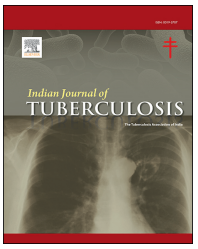

Case report

An interesting case summary of tubercular pneumonia masquerading as viral pneumonia kept on extra-corporeal membrane oxygenation

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ABSTRACT

Mortality in patients with pulmonary tuberculosis remains high, especially in those who develop acute respiratory distress syndrome (ARDS). We herein, report a case of 40 year old female, with ARDS due to severe pulmonary tuberculosis. She was admitted in the intensive care unit of a tertiary care centre. Owing to very poor ABG report, she was intubated and put on Mechanical ventilator support. Bronchoscopy was performed and BAL was extracted, which showed no growth. Further deterioration of gas exchange prompted the decision to put her on ECMO.

During her stay on ECMO, she developed massive inta-alveolar hemorrhage following which repeated bronchoscopic interventions were done to remove blood clots. BAL extracted on day 4 and day 8 showed growth of A. baumannii and *K. pneumoniae* respectively. But BALGeneXpert on day 8 came out to be positive for Mycobacterium Tuberculosis and subsequently ATT was added to her treatment regimen.

Her alveolar hemorrhage continued to worsen and subsequently ECMO was removed. After 12 days of hospitalization, she went on to develop bradycardia and could not be rescued. Though the patient's life was lost, this case provided many insights on the use of ECMO in the management of ARDS due to Pulmonary tuberculosis and it should be considered as one of the treatment options.

1. Introduction

Tubercular Pneumonia is an entity where endobronchial spread to lobar or multilobar locations result into air-space consolidation, further leading to nodular lesions. Tubercular Pneumonia can further lead to Acute Lung Injury. Acute lung injury [ALI] is a disorder characterized by inflammatory damage to the alveolar capillary membrane producing severe derangement of gas exchange, which could result from a

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variety of insults, ultimately resulting in severe hypoxemia, non-cardiogenic pulmonary edema, and the acute respiratory distress syndrome [ARDS].[2] In general, abnormalities of gas exchange are uncommon in pulmonary tuberculosis [TB] because concomitant involvement of ventilation and perfusion results in maintenance of the normal ventilation–perfusion relationship.[11] However, severe hypoxic respiratory failure due to ALI can sometimes complicate severe forms of pulmonary tuberculosis including military TB.[6,18,43] This complication is associated with a very high mortality despite treatment. Hence, early recognition and appropriate management of this uncommon complication is of utmost importance.

Even though acute respiratory failure (ARF) is well recognized complication in patients with PTB, sparse epidemiological data are available on this entity. In the study of Korea, Choi et al[1] found that 1.7% of 1010 patients with PTB had acute respiratory failure. The incidence is as high as 20% in military TB and 0.8% in tubercular pneumonia.[2] The incidence increases with delay in diagnosis and late institution of treatment therapy.[3] Study from Mumbai shows ARF due to TB accounted for 1.7% of admission in ICU.[4] A report from Chandigarh suggests 9 of 187 (4.8%) patients of Tuberculosis develop ARDS.[5] Sharma et al reported 1.06% of tubercular patients develops ARDS per year.[6] The reported mortality rate of TB associated with ARF requiring mechanical ventilation (MV) varies from 60 to 80%.[5]

Factors independently associated with mortality in TB pneumonia are advanced age, the presence of shock unrelated to sepsis, poor nutritional status and delay in the establishment of diagnosis and institution of specific therapy.[7]

There were many factors which predispose to ARDS in tubercular patient. Most common is malnutrition.[8–10] Others are alcoholism, diabetes, hypothyroidism, immunosuppressive conditions.[8,10–13]

Lung protective mechanical ventilatory support is the current standard of care for patients with ARF while veno-venous extracorporeal membrane oxygenation (VV-ECMO) is an accepted alternative option in refractory hypoxemic respiratory failure. VV-ECMO ensures adequate oxygenation and CO2 removal avoiding ventilator induced lung injury. The decision to continue prolonged VV-ECMO support can be difficult and challenging as limited data are available. In particular, the healing rate of TB pulmonary lesions is characteristically slow and, thus, the need for prolonged ventilator and non-ventilatory support modalities can be expected in cases of ARF secondary to TB. There are few reports of VV-ECMO for ARF due to TB,[7,14–17] probably because of low frequency of thiscomplication, but also due to cost and accessibility issues.

Here we describe the case of a middle age group woman with refractory respiratory failure caused by pulmonary TB, which was unresponsive to conventional MV and not even maintained on VV-ECMO support.

1.1. *Case report*

A 40-year-old Indian female was admitted to a tertiary care centre with chronic low grade fever and chronic cough of 15 days duration, and acute onset dyspnea (NYHA grade 4), tachypnoea and desaturation of 1 day duration. Patient was a known case of Type 2 Diabetes Mellitus and Hypothyroidism on replacement therapy. She had no past history of Tuberculosis.

On auscultation, she had bilateral extensive rales. At baseline she was desaturating and subsequently she was intubated and taken up on invasive ventilator support, AC/VC mode, high PEEP and low Tidal Volume strategy.

Her initial metabolic and hematological profile was consistent with anaemia and leucocytosis, for which she underwent blood transfusions and taken on higher antibiotics. Her ABG was consistent with Type 2 respiratory failure. Iron profile showed raised Serum Iron and deranged Total Iron Binding Capacity, while she also had hypoalbuminia and hyperbilirubinimea. Her chest x-ray at the time of admission was suggestive of bilateral confluent alveolar opacities partially sparing right upper zone. USG Chest was suggestive of minimal bilateral pleural effusion with air bronchogram in right lung. USG Whole Abdomen showed grossly enlarged liver with mild derangement of Liver Function test with raised Alkaline Phosphatase (Tables 1–5).

Her initial ECHO was suggestive enlarged Left Atrium with normal sized Left Ventricle and significantly diminished Left

Table 1 – Serial hemograms.

CBC	Day 1	Day 4	Day 8	Day 12
Haemoglobin	7.0	7.8	9.3	7.4
Platelet	3.27 lac	2.27 lac	1.78 lac	1.22 lac
TLC	23000	18000	13400	12500

Table 2 – Serial arterial blood gas analysis.

ABG	Day 1	Day 4	Day 8	Day 12
pH	7.247	7.410	7.451	7.423
PO_2	55	68	62.9	308
PCO_2	60.4	40.4	33.4	28.7
HCO_3	25.4	25.2	22.9	18.4

Table 3 – Serial renal and hepatic profile.

	Day 1	Day 6	Day 12
Urea	58	81	94
Creatinine	1.06	0.9	0.58
SGPT	19	18	12
SGOT	54	56	116

Table 4 – Acute phase reactants.

ESR	32→92
Pro Calcitonin	6→24
Ferritin	>1500

Table 5 – Total protein and bilirubin on day 1.

Protein/Albumin/Globulin/A:G	5.82/2.07/3.75/0.5
Total Bilirubin/Direct/Indirect	2.05/0.59/1.46

Ventricular Ejection Fraction (25%), however it recovered over course of her treatment. Her initial Trop I, CPKMB and PRO BNP were raised. These biochemical parameters along with echocardiographic findings arouse suspicion of Septic Cardiomyopathy (Table 6).

Her initial blood culture showed no secondary growth. She was also subjected to Bronchoscopy and her Broncho-alveolar Lavage showed no secondary growth. Endotracheal Tube culture sensitivity showed growth of Klebsiella.

Over the time of her stay, her imaging and respiratory acidosis kept on worsening despite using recruitment maneuvers, high PEEP-low tidal volume ventilation, prone positioning and sedation-paralysis (Figs. 1–4).

Owing to worsening imaging and respiratory acidosis, she was taken up on Veno-Venous extra corporeal membrane oxygenation, anticoagulation management being guided by aPTT based protocol (Table 7).

She also went on to develop oligo-anuria following which she was subjected to Renal Replacement Therapy.

Table 6 – Cardiac markers.

Trop I	1.321
CPK MB	18
Pro BNP	1714

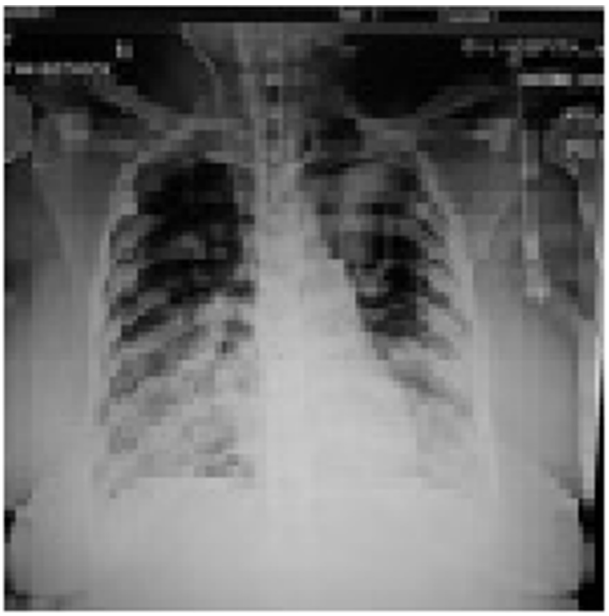

Fig. 1 – Chest Xray day 1.

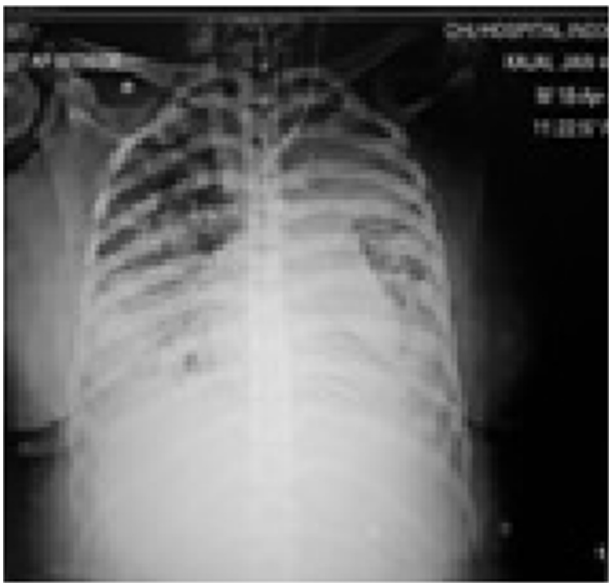

Fig. 3 – Chest Xray day 8.

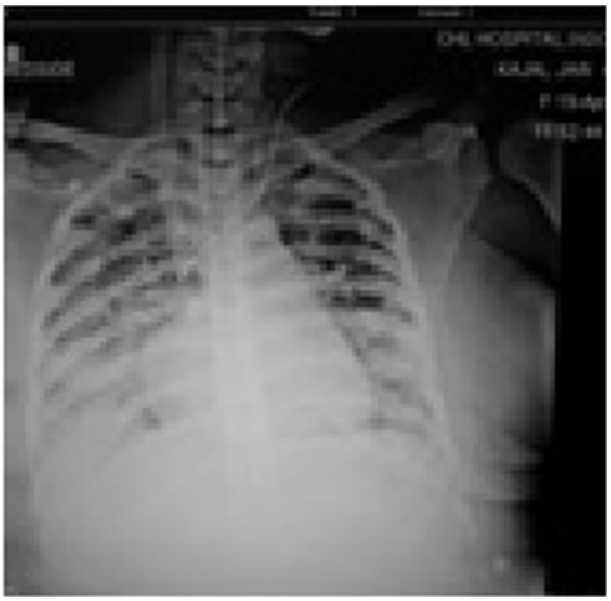

Fig. 2 – Chest Xray day 4.

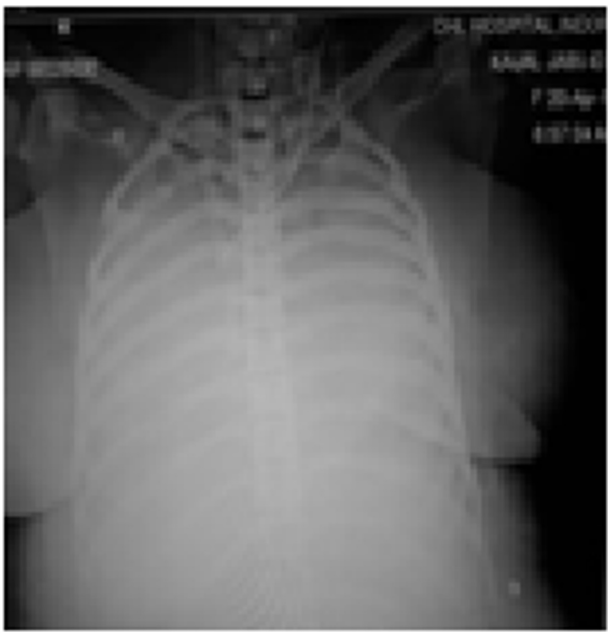

Fig. 4 – Chest Xray day 12.

Table 7 – Serial APTT monitoring.

	Day 1 ECMO	Day 2 ECMO	Day 3 ECMO	Day 4 ECMO	Day 5 ECMO	Day 6 ECMO	Day 7 ECMO	Day 8 ECMO
APTT	41.4	46.6	36.3	44.2	43.7	65.4	41.7	31.5

During her stay on ECMO, she developed massive intaalveolar hemorrhage following which repeated bronchoscopic interventions were done to remove blood clots. BAL extracted on day 4 and day 8 showed growth of A. baumannii and *K. pneumoniae* respectively. BALGeneXpert on day 8, also came out to be positive for Mycobacterium Tuberculosis and subsequently empiric ATT was added to her regimen.

Her alveolar hemorrhage continued to worsen and subsequently ECMO was removed. She went on to develop cardiac asystole following which CPR was initiated as per ACLS protocol, though she could not be revived and was declared deceased.

2. Discussion

Nodular lesions resulting from air-space consolidation due to endobronchial spread to lobar or multilobar locations is termed as TB pneumonia.[8] The onset of tubercular pneumonia, unlike that of classical form of pulmonary tuberculosis, typically has an acute clinical presentation, with cough, fever and chest pain, often being confused with and treated as common bacterial pneumonia. Thus in case of pneumonia, especially in regions where disease is prevalent, diagnosis of Tuberculosis should be considered.[42]

TB pneumonia can further complicate into acute lung injury. The development of ALI due to TB pneumonia was first reported in 1977 by Agarwal et al.[11] They reported 16 patients with acute respiratory failure, 10 of whom required mechanical ventilation. Alcholism and immunosuppressive conditions were the predisposing factors in almost all cases.

Fever, non-productive cough, chest discomfort and dyspnea are the common symptoms and the average interval between onset of symptoms and diagnosis is 14 days.[9,10] In more than 50 per cent of patients, the diagnosis of TB is not known at the time of admission with respiratory failure[8] like in the present case. A large proportion of these patients may harbour HIV infection.[3] Benatar et al suggested that in a patient with unexplained ARDS, a history of fever of more than 15 days duration and elevation of serum alkaline phosphatase should arouse the suspicion of TB as the underlying cause.[10] Raised ALP was found in our patient as well. Other reported clinical findings includehepato-splenomegaly, mild hepatic dysfunction and pancytopenia[9] though, in contrast our patient had leukocytosis. As in severe systemic sepsis, dysfunction of other organs is seen in 35% of patients with ARF due to TB even in the absence of other bacterial infections. These manifestations are encountered more often in miliary TB than in TB pneumonia. Mycobacterial infection itself can cause septic shock, with increased cardiac index, and low systemic vascular resistance.[20] Non-mycobacterial sepsis due to secondary infection may supervene in approximately 40 per cent of patients receiving mechanical ventilation.[8] as in our patient where A. baumannii and K. pneumonia were found in Brochoalveolar Lavage sample. A significant number of patients also have co-existing DIC.[9] Mortality in patients with DIC is close to 100%.[21]

Study conducted by Adele et al,[44] reported that hyperferritinimia is found in patients suffering from tuberculosis, which was also found in our patient. There was mild elevation of Serum Procalcitonin level in our patients, which also falls in line with study done by Huang et al,[45] which suggests mild elevation of Procalcitonin in Tuberculosis due to key roles played by both TNF-a and IFN-c in cellular host response.

Tubercular Pneumonia can further complicate into Acute Lung Injury, which is characterized by inflammatory damage to the alveolar capillary membrane producing severe derangement of gas exchange, which could result from a variety of insults, ultimately resulting in severe hypoxemia, noncardiogenic pulmonary edema, and the acute respiratory distress syndrome [ARDS].[2] In a study conducted by Sharma et al[6] 29 out of 2733 TB patients went on to develop ARDS, where 22 patients had Pulmonary TB and 7 had Miliary TB.

Acute lung injury is suspected in patients with severe hypoxaemia, bilateral extensive rales on auscultation, presence of bilateral confluent alveolar opacities on chest radiograph in patients with proven pulmonary TB or prolonged fever.[19,22,23] Arterial blood gas analysis will reveal a widened alveolar-arterial oxygen gradient and type I respiratory failure with normal or low arterial carbon dioxide tension [PaCO2] is usually seen.[22,23,25,26] The ratio of PaO2 to fraction of oxygen in inspired air [FIO2] is 200 or less, in the presence of criteria mentioned in American-European consensus conference (acute onset, bilateral infilterate on chest radiograph) is diagnostic of ARDS.[2,27]

Radiographic changes of ARDS may mask underlying TB and alveolar infilterates that are more organized or appear more nodular than usual.[24] Choi et al[1] systematically reviewed the chest radiographic and HRCT findings in 17 patients with ALI due to TB. During resolution, HRCT may reveal bilateral extensive thin-walled cystic lesions.[1] Chest radiographs show nodular lesions, with mixed consolidation and ground glass opacities.[8,18] High resolution computed tomography [HRCT] shows bronchogenic dissemination with ground glass attenuation.[19] The classical tree-in-bud appearance is seen on computed tomography [CT] in less than 50% of cases.[1]

This complication is associated with a very high mortality despite treatment and needs early recognition and appropriate management of this uncommon complication is of utmost importance.

Conventional treatment of ARF includes protective MV by limiting tidal volume[28] and lung recruitment maneuvers,[29] pursuing negative fluid balance[30] and adequately treating the cause. In a ten-year review of patients with TB requiring mechanical ventilation for ARDS, Penneret al[8] found that 50% of his cases had TB pneumonia. The mortality of ARDS patients with PTB requiring MV is relatively high compared with that of patients with ARDS from other causes.[33] The reported mortality rate of TB associated with ARF requiring mechanical ventilation (MV) varies from 60 to 80%.[5]

Table 8 – Previous Case reports of ARF due to Tuberculosis managed by ECMO.

Serial number	Sex	Age	Underlying condition	Treatment	Length of ECMO	Outcome	Author/year
1	F	58	None	None	5 days	Death	Homan W 1975[37]
2	F	15	None	INH/RFP/EB/PZA	6 days	Recovery	Petrillo TM 2001[38]
3	M	20	None	INH/RFP/EB/PZA	89 days	Recovery	Mauri T 2012[39]
4	F	14	Histocytic hemophagocytosis	INH/RFP/EB/PZA	6 days	Recovery	Monier B 2013[40]
5	F	24	Laryngeal papilloma	INH/RFP/EB/PZA	36 days	Recovery	Andresen M 2013[41]
6	M	20	None	INH/RFP/EB/PZA	89 days	Recovery	Cogliandro V 2014[42]

VV-ECMO is an alternative for management of catastrophic respiratory failure, which is indicated after high PEEP, low tidal volumeventilation, prone positioning and paralysis have failed to control hypoxemia or hypercapnia. ECMO is considered one of the treatment options for severeARDS.[14,15,31]

Five patients with acute respiratory failure due to PTB were recently reported to be successfully rescued by ECMO[17,34–38](Table 8).

An innovative aspect is the duration of ECMO, which was longer in Tubercular ARDS than due to other causes. The clinical courses of patients with PTB often become indolent and the healing rate of PTB is characteristically slow. A previous study reported that PTB patients with greater disease extent and severity showed persistent inflammation and required longer treatment.[39] While there is some concern that long-term use of ECMO may lead to a higher risk of complications, recent progress in the techniques and equipment used in ECMO have made prolonged ECMO support feasible.[40]

In the study reported by Sharma et al,[6] acute physiology and chronic health evaluation II [APACHE II] score greater than 18; APACHE II score less than 18 in the presence of hyponatraemia and PaO2/FIO2 ratio less than 108.5 were predictors of death in patients with TB-ARDS.

3. Conclusion

Overall mortality in ARF due to TB is between 40 and 80 per cent. Non-survivors of ARDS, regardless of the cause, die of respiratory failure in less than 20% of cases.[41] Most deaths are primarily related to the underlying disease, the severity of the acute illness, and the degree of dysfunction of other organs.[41] VV-ECMO can be used as an alternative therapy for refractory hypoxemia secondary to pulmonary TB. This is a potentially reversible condition, and the use of VV-ECMO plus anti-TB treatment along with corticosteroids may be life-saving in patient.

Conflicts of interest

All authors have none to declare.

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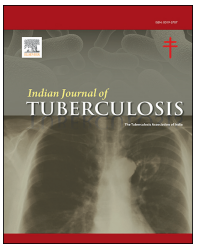

Case report

Gastric tuberculosis mimicking liver abscess – A case report

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Gastric malignancy

ABSTRACT

Tuberculosis of the stomach is quite rare, both as a primary or secondary infection. It has varied presentation ranging from non-specific abdominal pain and constitutional symptoms to hematemesis, gastric outlet obstruction and pyrexia of unknown origin. Here, we report a rare, interesting case of locally advanced gastric tuberculosis, which morphologically mimicked liver abscess initially in a young, immunocompetent patient presenting with fever and abdominal pain. The disease was diagnosed by GeneXpert MTB/RIF assay, and responded well to antituberculosis medication without surgery. Clinicians must bear in mind that, even in the absence of immunodeficiency, as in this case, tuberculosis can involve any site in the gastrointestinal tract and may present with a variety of presentation and infiltrating adjacent organ that might be mistaken as malignancy. This is first case report of gastric tuberculosis, which is locally advanced with adjacent liver infiltration initially thought to be left lobe liver abscess.

1. Introduction

Primary Tuberculosis (TB) of the stomach is rare (0.4%–2%) consequent to the bactericidal property of the gastric acid, scarcity of lymphoid tissue, rapid emptying and thick intact mucosa.[1] It is usually associated with pulmonary tuberculosis or with immunodeficiency state.[2] It has varied presentation as well as broad differential diagnosis. Here, we report a case of gastric tuberculosis, which morphologically mimicked various benign and malignant gastric conditions.

1.1. Case report

A 30-year-old man presented with epigastric pain, fever, and weight loss for 1 month. Ultrasonography done at other centre revealed solitary hypoechoic lesion in the left lobe of liver likely abscess. Based on this he was treated with anti-amoebic drugs and broad-spectrum intravenous antibiotics for 30 days with partial relief in symptoms but pain was persistent hence he came to us for second opinion. On examination, he was noted to be hemodynamically stable. The physical examination revealed epigastric ill-defined 5 × 8 cm mild tender lump

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inseparable from left lobe of liver. Laboratory studies were remarkable for a microcytic anaemia of 8.0 g/dL, leukocytosis 22800/μL, platelets of 378,000/μL, alanine aminotransferase 91 IU/L (upper limit of normal [ULN], 40 IU/L), aspartate aminotransferase 94 IU/L (ULN, 40 IU/L), bilirubin 0.8 mg/dL (ULN, 1.2 mg/dL), alkaline phosphatase 387 IU/L (ULN, 150 IU/L), A computed tomography (CT) scan of the abdomen with intravenous contrast was done for epigastric lump, which revealed asymmetrical gastric wall hypodense thickening with exophytic growth (solid arrow) with peri gastric lymphadenopathy and heterogeneously enhancing hypodense lesion in left lobe of liver (empty arrow) (Fig. 1). An upper endoscopy was subsequently performed and was remarkable for a diffuse nodular lesions in gastric body with surface erosion, reduced distensibility, pus extruding from nodule (Fig. 2). Repeated endoscopic biopsies were inconclusive other than chronic gastritis. This patient's gastric nodule biopsy for Xpert MTB/RIF assay showed *Mycobacterium tuberculosis* DNA, Rifampin sensitive. Targeted liver biopsy showed mixed inflammatory cell infiltrate of neutrophils, plasma cells, lymphocytes, occasional giant cells. After 9 months of anti-tubercular treatment (ATT) with Isoniazid, Rifampin, Ethambutol and Pyrazinamide his gastric as well as liver lesion responded significantly on CT scan (Fig. 3) and upper endoscopy (Fig. 4 {antrum} and Fig. 5 {body}).

2. Discussion

Our patient initially misdiagnosed as amoebic liver abscess based on ultrasonography and treated with multiple broad spectrum intravenous antibiotics. Secondly also misdiagnosed as neoplasms (lymphoma > adenocarcinoma) of stomach because of liver space occupying lesion (SOL) but repeated biopsies from stomach as well liver lesion were negative for malignancy so we ruled it out. Clinical picture also mimic as gastric lymphoma because of young age, fever, weight loss and gastric thickening but response to ATT ruled it out.

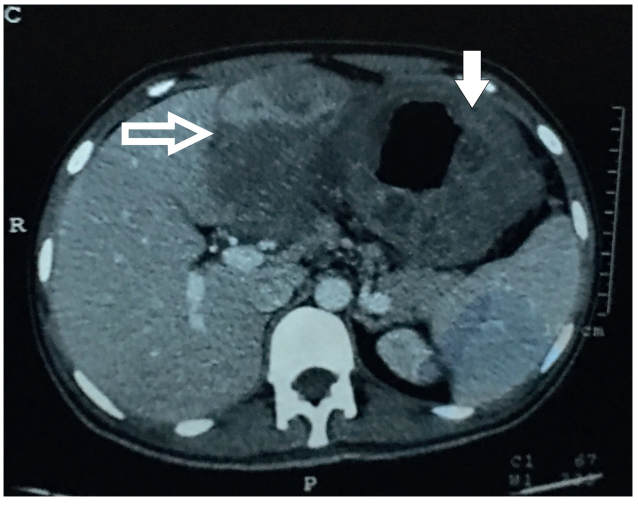

Fig. 1 – Computed tomography of abdomen showing heterogeneous gastric wall thickening with internal hypodense area (solid arrow) and adjacent left liver lobe infiltration by lesion(empty arrow).

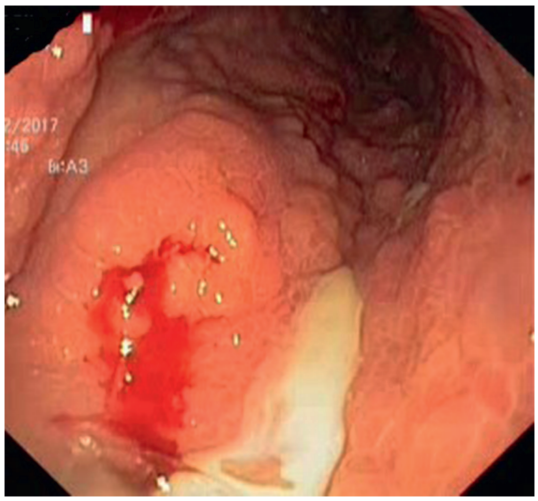

Fig. 2 – Gastroscopic image showing multiple nodules studded in body and antrum with pus exuding from one of nodule.

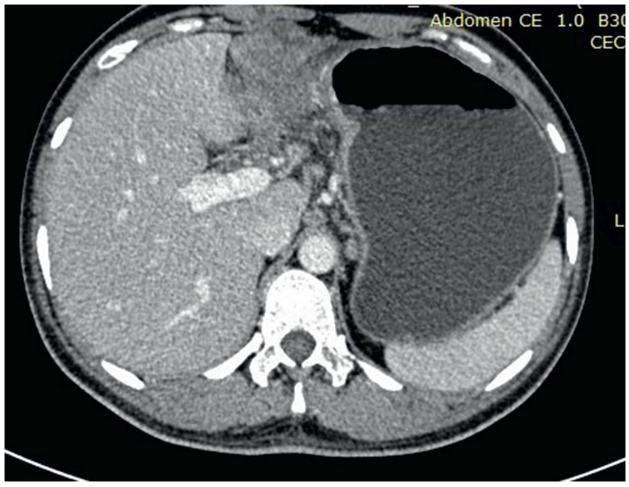

Fig. 3 – Post treatment computed tomography of abdomen showing significant resolution of both gastric as well as liver lesion.

Gastric tuberculosis (GTB) usually develops secondary to pulmonary tuberculosis. In a review of literature, Broders found evidence of pulmonary tuberculosis in 34 out of 49 cases of GTB.[3] Besides direct mucosal invasion of swallowed bacilli, the other routes of infection include retrograde spread from celiac lymph-nodes, hematogenous spread, direct extension or super – infection of a pre-existent gastric ulcer. There are very few reports of primary gastric tuberculosis i.e., without evidence of tuberculosis elsewhere. There are some case reports of gastric tuberculosis with unusual presentation like as hematemesis,[4] gastric outlet obstruction,[5] pyrexia of unknown origin,[6] dysphagia,[5] peptic ulcer disease[7] and advanced gastric cancer.[8] The diagnosis of GTB can be confirmed by demonstrating caseating granulomas and/or acid fast bacilli in the mucosa and sub-mucosa of the

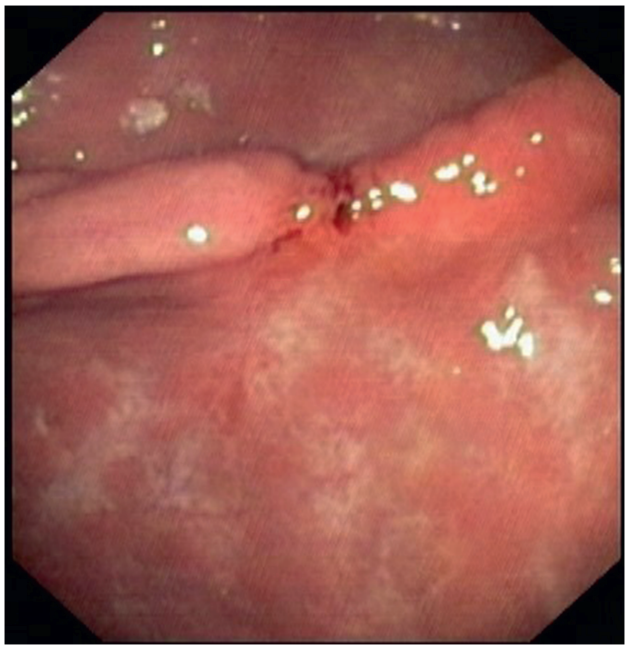

Fig. 4 – Post treatment gastroscopic image of body showing resolution of stomach nodule.

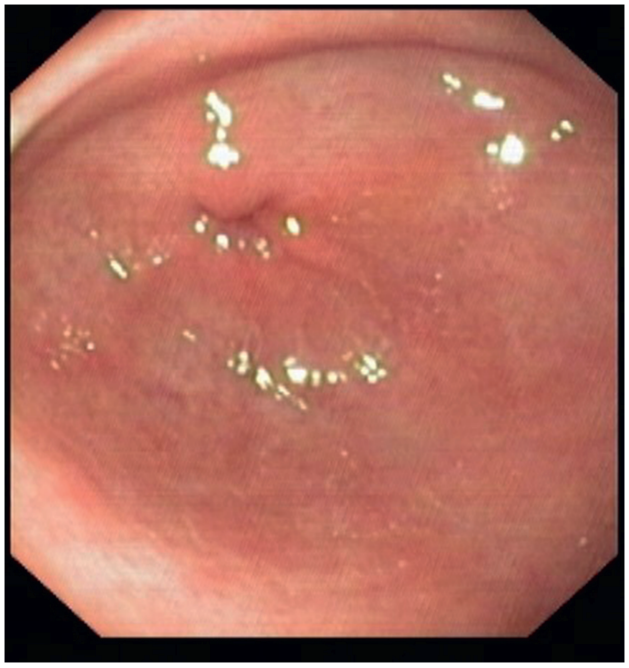

Fig. 5 – Post treatment gastroscopic image of antrum showing resolution of stomach nodule.

stomach. But endoscopic biopsy rarely reveals granulomas in gastric TB because of the predominantly submucosal location of these lesions.[9] GeneXpert MTB/RIF is newer nucleic acid amplification based technique to detect *M. tuberculosis* along with Rifampicin sensitivity pattern, which gives result within 2 hours. This patient also highlights importance of Xpert MTB/RIF assay in diagnosing TB, which particularly obviate the necessity of operation.

GI tuberculosis responds well to chemotherapy. Although six months duration of therapy has been shown to be effective for GI tuberculosis, the duration is best individualised and guided by the response to treatment. Surgery is usually required if gastric outlet obstruction is present.

3. Conclusion

Gastrointestinal TB can have varied presentation ranging from non-specific abdominal pain to catastrophic intestinal perforation. Although uncommon but can present like locally advanced gastrointestinal lesion infiltrating adjacent solid organ like liver that may be confused with other inflammatory, infective or neoplastic conditions so high index of suspicion is required for early diagnosis particularly in TB endemic countries like India.

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Conflicts of interest

The authors have none to declare.

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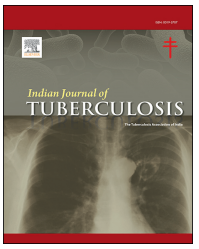

Case Report

Discrepancy between ventricular and lumbar CSF in chronic meningitis

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ABSTRACT

Meningitis patient can present with various manifestation including hydrocephalus due to multiple reason. Diagnosis of meningitis mainly rely on CSF analysis which is usually obtained from lumbar puncture. In case of hydrocephalus CSF can be obtain from ventricles during VP shunt operation. Sometimes ventricular CSF can be normal in meningitis patient while lumbar CSF shows abnormality. Possible mechanisms behind this phenomenon are discussed here. Patients who present with hydrocephalus and have normal Ventricular CSF should investigated with lumbar CSF analysis in a view of delay in diagnosis and treatment.

1. Introduction

Meningitis is inflammation of coverings of brain and spinal cord. Raised intracranial pressure can be part of clinical presentation in acute or chronic meningitis. Brain edema, cerebral infarction, venous thrombosis, hydrocephalus or combination of them are conditions responsible for raised ICP in meningitis.[1] Out of them hydrocephalus is commonly associated with raised ICP. Diagnosis of meningitis can be confirmed by CSF fluid analysis which usually obtain from lumbar puncture. In case of acute hydrocephalus urgent placement of external ventricular drainage is required to relieve raised intracranial pressure.[2] In such cases CSF can be obtained during the operation to be examined. Sometime this CSF results come out to be normal which leads to unnecessarily delay in diagnosis and treatment.[3] We are reporting here a case of chronic meningitis in which initial CSF obtain from ventricular drainage was normal. Patient had persistent headache and occasional vomiting despite functioning VP shunt. Repeat CSF has done from lumbar puncture shows finding suggestive of chronic meningitis (see Figs. 1 and 2).

2. Case report

35 year old male presented with 15 days history of moderate intensity generalized dull aching headache with vomiting along with low grade fever. There was no history of altered sensorium, abnormal behavior, seizure or other focal deficit. CT head showed communicating hydrocephalus. Patient was operated for ventriculo-peritoneal shunt and ventricular CSF fluid was sent for investigation. CSF study revealed 5 cells with lymphocyte predominance with protein 15.18 mg/dl and sugar 64.5 mg/dl. After VP shunt patient improved symptomatically and discharged with conservative treatment. Three months after operation patient presented to us with complaint of

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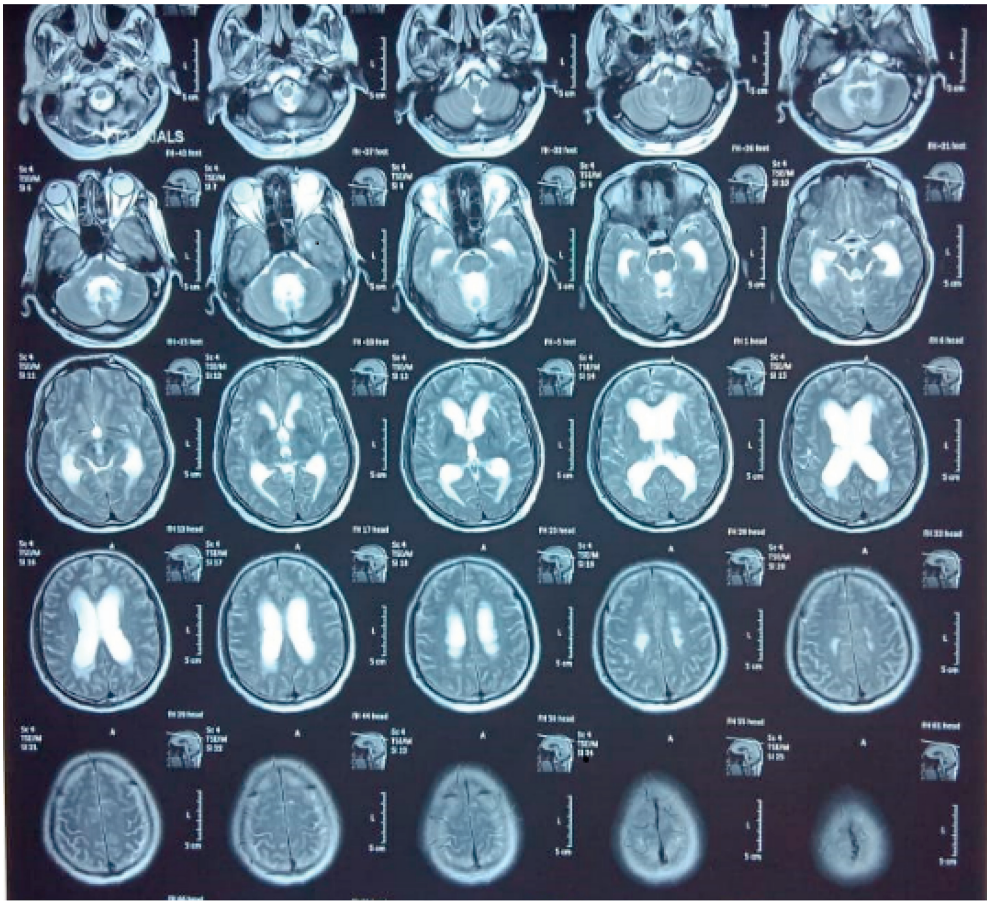

Fig. 1 – T2 weighted MRI suggestive of hydrpcephalus (Before VP shunt when ventricular CSF obtained).

persistent headache with occasional vomiting which started 10 days ago. Again there was no history of altered cognition. Relative gave history of repeated analgesic ingestion for headache during previous 3 months. On examination patient was conscious and oriented to time, place and person. There was no cranial nerve abnormality. Motor, sensory and cerebellar examination was normal. Mild terminal neck rigidity was present. After history and examination possibility of shunt dysfunction or chronic meningitis was considered. Investigation revealed microcytic hypochromic anemia with normal leukocyte and platelet count. Renal function test, liver function test, serum electrolytes were normal. C-reactive protein was positive and Erythrocyte Sedimentation Rate was 110. CT brain showed VP shunt in situ without hydrocephalus or parenchymal abnormality Figs. 1. CSF analysis was done by lumbar puncture showed total count of 200 with lymphocytic predominance (70%) with protein of 198 mg/dl and sugar was 76 mg/dl. CSF adenosine deaminase level was 16.4. MRI Brain was suggestive of multiple small subacute infarct involving right frontotemporal, left frontal and cerebellum Figs. 2. In view of clinical picture and investigation findings patient was considered as having chronic meningitis and started with anti-tubercular medication and steroids. After starting treatment headache symptomatically improved in next 2 weeks of follow up.

3. Discussion

Formation of CSF predominantly occurs in choroid plexus of cerebral ventricles. After formation CSF circulate through cerebral ventricles with part of it also flows around spinal cord and ultimately returns to subarchnoid space where it reabsorbs into sagittal sinus. Any derangement in this process due to any pathological condition leads to formation of hydrocephalus.[2] studies comparing ventricular and lumbar CSF are limited because of technical and ethical difficulties associated with obtaining ventricular CSF in whom VP shunt or surgery is not being done. As observed in our case there is a discrepancy between ventricular and lumbar CSF contents in meningitis patient though timing of both the investigation was different. In physiological condition also there is difference between ventricular and lumbar CSF content. In normal CSF protein content tends to increase by almost 60% from ventricular to lumbar (mean 26 mg/dl vs 42 mg/dl).[4] This difference used to increase in CNS infection due to impairment of blood brain barrier and increase protein content slows down CSF in lumbar sac which alters CSF composition. Opposite to that glucose concentration is in decreasing trend from ventricles to lumbar due to consumption by leukocytes and bacteria.[5] there is very limited literature comparing

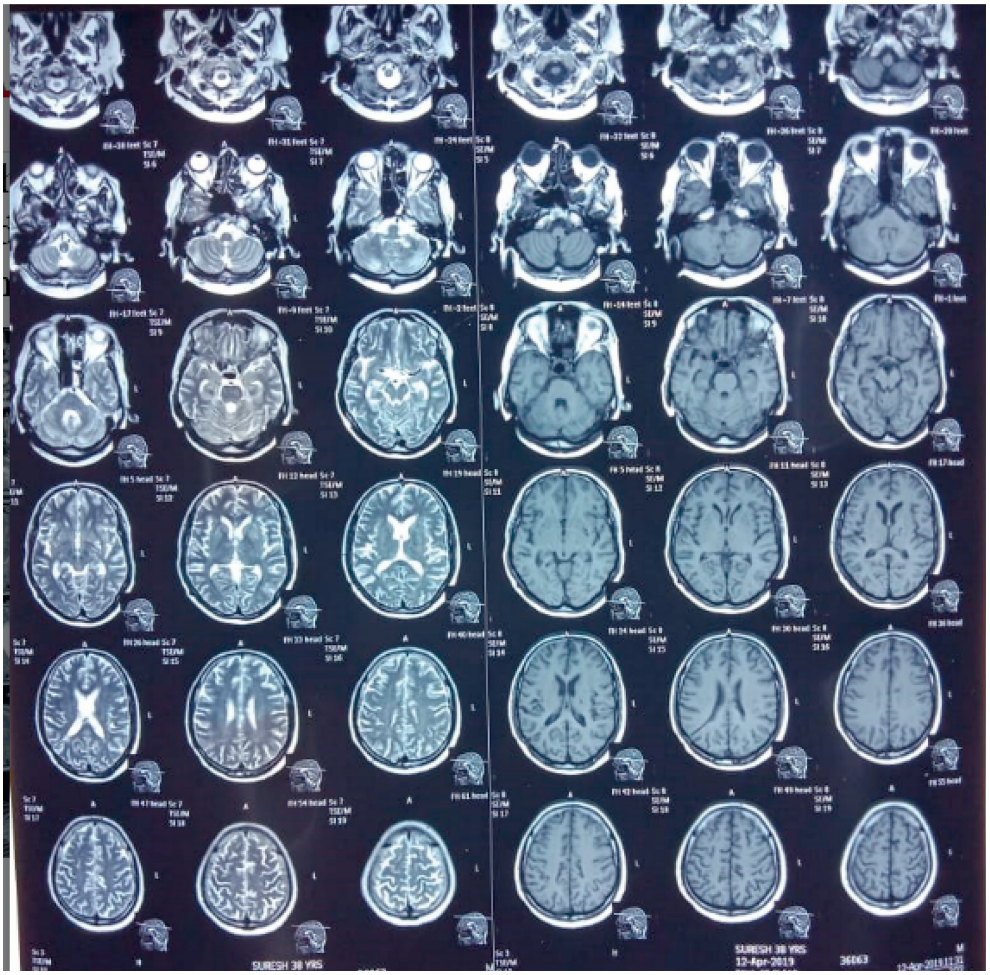

Fig. 2 – T1 and T2 weighted images showing resolved hydrocephalus (after VP shunt when LP done).

leukocyte count between ventricular and lumbar CSF which shows existence of some cranio-caudal gradient in counts.[6]

There are few reasons described behind discrepancy between ventricular and lumbar CSF in CNS infection and one of them is exaggeration of existing cranio-caudal gradient in CSF content as discussed above. Other reason considered is compartmentalization of subarachnoid space caused by infection.[7] Difference in CSF from these compartment can be attributes to location of infective focus. High leukocyte and protein content can block the foramens in CSF circulation and arachnoid villi which leads to decrease in reabsorption and hydrocephalus. Blockage of foramina of luschka and magendie would result in discrepancy between ventricular and lumbar CSF and can be other reason.[2] Lastly it can be though that as CSF is formed in ventricles leads to alteration in ventricle CSF concentration by diluting with normal CSF in case where choroid plexus is not involved in infective process.

Diagnosis of meningitis predominantly based on CSF analysis which is usually obtains by lumbar puncture. In 10% of meningitis cases CSF can be normal which may be attributes to duration of disease and precocity of lumbar puncture.[3] In case of patient who presented with impaired consciousness and hydrocephalus sometime lumbar puncture is deferred due to risk of cerebral herniation.[1] In such cases ventricular CSF can be obtain while performing VP shunt operation at the time of insertion or from external ventricular drainage. This may result in normal CSF despite of infective meningitis due to reasons discussed above and would lead to delay in diagnosis and treatment as occurred in our case. Timing of ventricular and lumbar CSF was different in our case, but by the time hydrocephalus develops in chronic meningitis, lumbar CSF is invariably abnormal. So, in strongly suspected case of meningitis lumbar CSF analysis should be done despite normal initial ventricular CSF.

4. Conclusion

Our case highlights that difference between ventricular and lumbar CSF can be present in chronic tubercular meningitis

patients. Early diagnosis and appropriate treatment can make significant impact on morbidity in meningitis patient. It is advisable to do lumbar CSF in suspected case of meningitis even if ventricular CSF is normal to avoid risk of delay in diagnosis and treatment.

Conflicts of interest

All authors have none to declare.

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