ORIGINAL ARTICLE

Study on Tuberculosis Treatment and Drug Resistance Testing in a Tertiary Care Center in Central India

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Abstract

National TB Elimination Program (NTEP) in India has planned for free of cost diagnosis and treatment for tuberculosis (TB) patients. This study is carried out to find out the deficiencies in treatment prescribed by practitioners, whether they were as per NTEP guidelines or not, and to assess the use of cartridge-based nucleic acid amplification test (CBNAAT) by practitioners for the detection of rifampicin resistance as per the current guidelines.

Aims and objectives: This study was conducted to see the deficiencies in treatment prescribed by practitioners, whether they were as per NTEP guidelines or not, and to assess the use of CBNAAT by practitioners for the detection of rifampicin resistance as per the current guidelines.

Materials and methods: The doctor's prescription of a total of 199 patients who visited the outpatient department (OPD) were assessed, and data was collected as per inclusion and exclusion criteria.

Results: Out of the total 199 prescriptions, 83.4% of patients were prescribed antitubercular treatment (ATT) under directly observed treatment short course (DOTS), while in the remaining 16.6% of patients non-DOTS ATT [57% prescribed fixed dosage combination (FDC) and 43% prescribed individual drug] were prescribed by practitioners. CBNAAT was prescribed by only 52.8% of practitioners for TB diagnosis and drug resistance.

Conclusion: The method of prescribing non-DOTS ATT prescription drugs was not as per NTEP guidelines, and CBNAAT prescription was also less.

Keywords: Directly observed treatment short course, National tuberculosis elimination program, Nondirectly observed treatment short course, Revised national tuberculosis control programme, Tuberculosis, Xpert mycobacterium tuberculosis/cartridge-based nucleic acid amplification test/Trunat.

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Introduction

Drug-resistant TB (DR-TB) means mycobacteria is resistant to one or more ATT drugs. Inadequate or inappropriate drug administration (single drug administration in the form of monotherapy, irregular, or interrupted treatment) is mainly responsible for acquired drug resistance.

To fulfill the aim of elimination of TB, it is essential for every health practitioner to follow the guidelines laid by NTEP in India, formerly called Revised National TB Control Programme. Once TB diagnosis is established by the treating physician, it is required that the treating physician should prescribe the treatment as per NTEP guidelines and should avoid using drugs which do not fall in that treatment category of the patient, like avoiding using second-line drugs (fluoroquinolones) along with first-line drugs. Changes in NTEP treatment guidelines—(1) FDC ATT drugs for drug sensitive TB from December 2018; (2) no injectables for treatment of TB (even DR-TB) from December 2018; (3) change of weight band.

Approximately 3.4% of cases of newly detected TB in the whole world and 18% of cases among previously treated TB had either rifampicin-resistant TB or multidrug-resistant TB.[1]

Under NTEP, free diagnosis and treatment are offered to all TB patients. All TB patients are offered CBNAAT/Trunat test to detect TB and rifampicin resistance. It was introduced by the World Health Organization (WHO) in December 2010 and came into effect in India in 2012.[2]

This test is a recently introduced polymerase chain reaction (PCR) based method which detects the *Mycobacterium tuberculosis* bacilli (MTB) and it is resistant against rifampicin by targeting rpoB gene of MTB. CBNAAT is specific for MTB and gives results within 90 minutes.

Being a PCR-based method, it has shown a sensitivity of 59.5% and specificity of 99% on a single sputum specimen of culture positive patient.[3]

Xpert MTB/resistance to rifampin(RIF)®/CBNAAT is useful in detecting simultaneously TB bacilli and resistance to rifampicin. WHO also recommends CBNAAT as the first test for diagnosis of TB in all persons with presumptive TB.[4]

Xpert MTB/RIF assay can detect 131 bacilli in 1 mL sputum sample.[5] It has a sensitivity of 89% and specificity of 99% for pulmonary TB.[6] Sensitivity of Xpert MTB/RIF is different in different extrapulmonary cases, having the highest sensitivity in lymph node biopsies (83.1%), cerebrospinal fluid (80.5%), and low sensitivity in the pleural fluid specimen (46.4%).[7] Hence this assay can be used

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only as a diagnostic tool, but not for monitoring the treatment response. High operating costs, the requirement for continuous electric supply, and unable to sustain high temperature limit the widespread use of this technique.[8]

Hence this study provides information about the number of practitioners who were following the NTEP treatment guidelines and also the number of practitioners prescribing the CBNAAT test in pulmonary and extrapulmonary samples for determining ATT drug resistance.

Materials and Methods

A study of total 199 cases was done as a cross-sectional, observational study at a tertiary care center in Central India for 1 year and included the patients coming to various OPDs with the prescription of practitioners. Due to the coronavirus disease 2019 (COVID-19) pandemic, only this many cases could be studied. Prescriptions of both government and private practitioners were evaluated. These prescriptions were evaluated to see how many of the practitioners are treating TB as per the NTEP guidelines, how many of the practitioners have decided to go for the CBNAAT test, and the type of samples in which the practitioners have advised for the CBNAAT test.

Inclusion Criteria

Patients coming with a medical prescription from allopathic medical practitioners to various OPDs of the institution, who were started on ATT drugs on any of the clinical/radiological/microbiological basis. Prescription should be from the practitioner with an MBBS or higher degree holder (of any specialty) in the field of allopathic medicine.

For the purpose of the study, any prescription which is included should have any of the below-mentioned information.

- The prescription contained one or more first-line anti-TB drugs—isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin.
- Any other combination of first or reserve-line ATT drugs.
- The prescription of a combination of more than one reserve-line anti-TB drug.
- The prescription mentioned the diagnosis as "TB."

Exclusion Criteria

- Prescriptions of nonallopathic degree practitioners.
- Prescriptions in which drugs which are also used as antibiotics other than as anti-TB drugs, such as fluoroquinolones alone, were present.
- Prescription not older than 1 month since the date of starting the study, as we wish to study the recent changes of the NTEP guidelines in these prescriptions.

For the purpose of enrolling in the study we have randomly screened all patients attending OPDs and selected those patients who have fulfilled the inclusion and exclusion criteria and are ready to give the written informed consent. Only those prescriptions are considered for the study which were written not before 1 month prior to the start of study, for the reason that we wish to study the prescription were according to the recent changes in the NTEP.

Ethical Issues

The study was conducted after getting written informed consent from the patient prior to enrolling them for the study and was approved by Institutional Ethics Committee.

Data Collection and Analysis Method

All the data is recorded by using a structured *pro forma* and has been tabulated in a Microsoft Excel sheet. The data collected in the study has been statistically analyzed using Statistical Package for the Social Sciences 23.0 software.

Observation and Results

This study was carried out at the pulmonary medicine department at a tertiary care center of Central India. Data were collected from the patients coming to the various OPDs with ATT drugs prescription and who were started on ATT drugs as per the inclusion and exclusion criteria. A total of 199 patients were included in the study and were studied as per the inclusion criteria. Prescriptions of 120 males and 79 females were studied, having major study group ages ranging between 20 and 40 years (Table 1). Out of the total 199 prescriptions, 83.4% of patients were prescribed ATT under DOTS by the treating physician, while in the remaining 16.6% of patients non-DOTS ATT were prescribed by the treating physician. Among the non-DOTS prescription, 57% prescribed FDC non-DOTS drugs, while the remaining 43% prescribed individual drugs, and all the non-DOTS ATT prescriptions (16.6%) were not in line as per the NTEP weight band and dose format. Fluoroquinolones were prescribed as a part of the initial ATT treatment in 13% of the non-DOTS ATT drugs prescription. A CBNAAT test was prescribed for the detection of drug resistance in 52.8% of patients, with total pulmonary samples at 43.7%, and total extrapulmonary at 9%. Among the extrapulmonary samples, three samples were of pleural effusion, five samples were from lymph node, three samples were from gastric aspirate, one sample was for neurological TB, and six samples were from bone TB (Table 2).

Discussion

India has the highest TB burden in the whole world, with the approximated incidence of 2.69 million cases as per WHO in 2019.[9] Sputum smear examination is a very simple, specific, rapid, and inexpensive tool to detect acid-fast bacilli (AFB) for diagnosis

Table 1: Description of gender and age distribution

Gender		
Male	120	60.3%
Female	79	39.7%
Age (in years)		
<20	39	19.6%
20–40	93	46.7%
40–60	42	21.1%
>60	25	12.6%

Table 2: Description of treatment category given and the CBNAAT prescription

Treatment		
DOTS*	166	83.4%
Non-DOTS	33	16.6%
CBNAAT**		
Prescribed (Pulmonary + extrapulmonary samples)	105 (87 + 18)	52.8%
Not prescribed	94	47.2%

*Directly observed treatment short course; **cartridge-based nucleic acid amplification test

of pulmonary TB but it has low sensitivity. Overall sensitivity of sputum AFB, even in good settings, is only 60%.[10–12] Sensitivity of smear microscopy (SM) is further decreased in patients having extrapulmonary TB, small children and patients having coinfection of human immunodeficiency virus/TB.[13]

World Health Organization (WHO) recommended the CBNAAT as a bona fide test from 2010 because of its high quality performance in comparison to SM, especially in smear-negative cases.[14] WHO has advised using CBNAAT as a rapid diagnostic test for TB diagnosis and has prioritized areas like DR-TB. Universal drug susceptibility testing has been rolled out across the country since January 2018.[15]

Sputum microscopy had low sensitivity (9.3%), as also found by Geleta et al.[16]

Thrice weekly ATT drug regimen was being used till 2016, but now a daily regimen with FDC is being used for the treatment of drug sensitive TB so that ATT drugs can be given in appropriate weight bands.[17]

The weight band for the use of FDCs has been revised for the patients in each weight band as per WHO recommendation by the Technical Expert Group for TB treatment.[18]

In NTEP, for adult patients, 4-FDC [used in intensive phase (IP)] and 3-FDC [used in continuation phase (CP)] are being used.

The 4-FDC has a combination of isoniazid, rifampicin, pyrazinamide, and ethambutol drugs, and 3-FDC has combination of isoniazid, rifampicin, and ethambutol. For pediatric patients, dispersible 3-FDC and 2-FDC are being used. The 3-FDC has combination of isoniazid, rifampicin, and pyrazinamide, and 2-FDC has combination of isoniazid and rifampicin. The latest change in isoniazid (H)—mono/poly resistance regimen involves the complete omission of injection Kanamycin (Km) from both the pulmonary and extrapulmonary cases. And also, the total duration of the regimen will be 6 months, having no separate IP or CP. This new regimen will have all the old drugs levofloxacin, rifampicin, and pyrazinamide except the injectable Km.[19]

The purpose of this study is to observe whether the prescription of practitioners for the treatment of TB is as per the NTEP guidelines or not, and also assessment of using the CBNAAT test by practitioners for the detection of DR-TB. In our study, the CBNAAT test was prescribed in 105 prescriptions among the total 199 prescription (52.85%). In a similar study conducted by Sreekanth et al., the CBNAAT was prescribed in 107 cases among 337 cases (31%).[20] In another study conducted by Sethumadhavan et al.,[21] the CBNAAT was prescribed in 58 (23.2%) specimens among a total patient sample size of 250.

In our study, the CBNAAT prescription in the extrapulmonary samples was found to be 9%. In a similar study conducted by Gupta et al., the CBNAAT test prescription rate was 16%, that is, 12 cases of 72 in MTB detected cases from the total extrapulmonary sample size of 300.[22] In a similar study conducted by Kandi et al., the CBNAAT test prescription was found to be 45% in extrapulmonary samples.[23]

The reasons for not giving treatment according to the latest NTEP guidelines are—lack of awareness among the practitioners about new treatment guidelines, their past experience from treating TB (use of injectables and fluoroquinolones), and the use of patient friendly drug regimen (underdosing to avoid possible side effects like nausea and vomiting). The reason for less use of the CBNAAT test by practitioners are—less awareness of using the test and less knowledge regarding the utility of the test.

In a study conducted by Kakad et al., among 250 doctors, 82 doctors were not aware of the CBNAAT and 60 doctors were aware of the CBNAAT but did not prescribe it because of no knowledge regarding its sensitivity, specificity, and utility.[24]

Limitation

The current study was done at a tertiary care center where we get patients who are not managed by hospitals at the secondary level. A total of 199 patients were included in the study. Due to the COVID-19 pandemic, only this many cases could be studied. To get more specific data, more prescription of doctors at primary and secondary care centers has to be evaluated.

Conclusion

Tuberculosis (TB) is still a major problem in our country. The government is doing every possible effort to eliminate TB from our country, but it is not possible until the practitioners will not follow the guidelines laid by NTEP for the diagnosis and treatment of TB. We found in our study that both DOTS and non-DOTS regimen is being used for treatment. Methods of prescribing non-DOTS ATT drugs were found not appropriate as per NTEP guidelines as all the prescriptions were inadequate as per the drugs regimen started (FDC vs individual drugs) and drug dose given. The study also concluded that the CBNAAT test prescription is very low, which is not as per the latest NTEP guidelines of using the CBNAAT test in every suspected or confirmed TB patient to rule out drug resistance in both pulmonary and extrapulmonary samples.

In order to overcome all these problems, the government needs to implement these guidelines more strictly, also, regular conferences and various continuous medical education (CMEs) have to be organized at all health facility levels to keep the practicing doctor updated and motivated about following the latest guidelines, and also such conferences and CMEs have to be made mandatory to attend.

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