ORIGINAL RESEARCH PAPER

Pulmonary Medicine

PRIMARY DRUG RESISTANT TUBERCULOSIS - THE CONCERN!

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ABSTRACT

Tuberculosis is an airborne infection caused by mycobacterium tuberculosis. About 480000 people worldwide developed MDR TB in 2015, additionally 1,00,00 developed resistance to rifampicin and needed MDR TB treatment. MDR TB burden largely falls on China, India & the Russian Federation - which together account for nearly half of the global cases. The proportion of DR-TB cases among new cases is 2-3% and that among previously treated cases is 12-17%. **Aims and objectives:** To find the incidence of primary MDR TB in a tertiary care center in Navi Mumbai. **Materials & Methods:** A retrospective study of Culture and sensitivity reports of 100 patients was conducted. All underwent smear examination for AFB by ZNCF method. AFB Gene Xpert (CB-NAAT) and AFB culture and drug sensitivity. **Results-** In our study we found primary MDR to be 10 % while an additional 1 % was resistant to INH alone. All patients were HIV negative. **Conclusion-** The high proportion of Primary MDR-TB found in our study compels us to suggest that modalities to diagnose primary drug resistance tuberculosis should be made available to all newly diagnosed TB patients, irrespective of HIV status.

INTRODUCTION:

Tuberculosis is an airborne infection caused by mycobacterium tuberculosis, transmitted by inhalation of infected droplet nuclei. According to WHO, there were 10.4 million new cases of TB in 2015 [1]. The incidence in India is reported to be 2.2 million. Tuberculosis is one of the top 10 causes of death worldwide. In 2015, 1.8 million people died due to TB, including 0.4 million among people with HIV. Over 95% of TB deaths occur in low- & middle-income countries.

About 480000 people worldwide developed MDR TB in 2015. In addition, around 1,00,000 developed resistance to rifampicin and needed MDR TB treatment. The MDR TB burden largely falls on 3 countries- China, India & the Russian Federation - which together account for nearly half of the global cases. About 9.5% of MDR TB cases had XDR TB in 2015 [2].

There are two types of drug resistance - [3]

Primary drug resistance develops in patients who become infected with a resistant strain without ever having been treated with anti-tuberculosis drugs.

Acquired drug resistance was defined as the acquisition of resistance to anti- tuberculosis drugs by the organisms through selective multiplication of the spontaneously emerged resistant mutant fraction of the bacterial population as a result of inadequate chemotherapy.

The proportion of DR-TB cases among new cases is 2-3% and that among previously treated cases is 12-17% [4], which is one of the greatest public health challenges we face today. The extent of MDR TB is difficult to estimate because culture sensitivity is not a routine test especially in HIV negative newly diagnosed cases especially in developing countries.

Preventing initial infection with MDR TB and managing the treatment existing cases appropriately are the keys to containing the spread of this disease.

The present study was undertaken to estimate the incidence of primary MDR TB with an aim to diagnose MDR TB at the earliest to minimize spread of infection in the community

Aims and objectives:

1. To find the incidence of primary MDR TB in a tertiary care center in Navi Mumbai.

Materials & Methods:

A retrospective study was conducted in the department of pulmonary medicine at TMC, Navi Mumbai. Culture and sensitivity reports of 100 patients above the age of 15 years, diagnosed as pulmonary and extra pulmonary TB (pleural effusion and lymph nodes) were analyzed and compared with smear examination and AFB Gene Xpert (CB-NAAT).

All patients had undergone smear examination for AFB by ZN staining method at the RNTCP designated microscopy center. AFB Gene Xpert (CB-NAAT) and AFB culture and drug sensitivity were done at accredited laboratories. AFB culture was done using Bactec MGIT 960 TB system by rapid detection and continuous monitoring using Fluorescence method.

DISCUSSION -

In 2015 there were 10.4 million new (incident) TB cases worldwide, of which 5.9 million (56%) were among men, 3.5 million (34%) among women and 1.0 million (10%) among children. Six countries accounted for 60% of the new cases: India, Indonesia, China, Nigeria, Pakistan and South Africa [5].

India accounts for one fourth of the global TB burden. In 2015, an estimated 28 lakh cases occurred and 4.8 lakh people died due to TB. India has highest burden of both TB and MDR TB based on estimates reported in Global TB Report 2016.

An estimated 1.3 lakh incident multi-drug resistant TB patients emerge annually in India which includes 79000 MDR-TB Patients estimates among notified pulmonary cases. India bears second highest number of estimated HIV associated TB in the world.

MDR-TB cases in the SAARC region range from less than 1- 4% among new cases [6]. An estimated 1.1 lakh HIV associated TB occurred in 2015 and 37,000 estimated number of patients died among them [7]. Another study conducted in Vladimir region, Russia 2012 showed that 23% of new TB cases were resistant to Rifampicin[8].

A study conducted in a tertiary care hospital in South India showed MDR TB among new sputum positive Pulmonary TB cases to be 1% which was similar to other Indian studies[9].

A study conducted by Malhotra et al in Jaipur found that primary drug resistance to INH was 13.6% and to rifampicin was 6.8% [9]. In a study by Hamsse et al, MDR-TB among new cases was 2.4% [10].

In our study we found primary MDR to be 10 % while an additional 1 % was resistant to INH alone which was significantly higher when compared to most of the previous Indian studies. Of the primary DR TB, 4 were males & 7 were females. All patients were HIV negative.

Globally there was a 4.3 million gap between incident and notified cases, with India , Indonesia and Nigeria accounting for almost half of this gap[11].

The sustainable Development Goals (SDGs) for 2050 were adopted by united nations in 2015. One of the targets is to end the global TB epidemic. The WHO end TB strategy, approved by the World health Assembly in 2014, calls for a 90% reduction in TB deaths and an 80% reduction in the TB incidence rate by 2030, compared with 2015 [5].

Thus, the top priority for the control and, ultimately, elimination of MDR tuberculosis is prevention of its emergence [12]. Once MDR tuberculosis has emerged, however, urgent measures are required to curb its effects on efforts to control the disease.

As a result of inadequate measures of infection control, there is ongoing transmission of MDR tuberculosis and XDR tuberculosis in health care facilities and congregate settings (e.g., prisons) [13]. To date, virtually no country with a high burden of tuberculosis has implemented systematic measures to reduce the risk of tuberculosis transmission in health facilities [14].

Considering the high prevalence of primary drug-resistant TB among new smear- positive cases, standardized short-course chemotherapy may result in inadequate treatment, generating MDR-TB, which in turn increases the transmission of drug resistant TB strains [15,16]. We concur with the findings of a study conducted by Wang et al which emphasizes that all new smear-positive TB cases should be screened with DST to identify drug-resistant TB and MDR-TB, and, if possible, rapid DST diagnostics should be implemented to reduce transmission of drug-resistant TB. The findings of this study consolidate that infection control should be considered as priority strategy to address drug-resistant TB in China [17]. In our opinion considering the incidence of primary drug resistance tuberculosis in India stringent infection control measures should also be emphasized in our country. In a study conducted by Stephanie Law et al in Montreal the tuberculosis transmission model projected   minor changes in overall risk of infection, incidence, or prevalence of tuberculosis in India over 20 years, given current use, and frequency of inappropriate management practices by patients and providers within the different health sectors.

However, if these practices are not corrected, they project the tuberculosis epidemic will shift gradually from one that is predominantly drug susceptible to one with increasing drug resistance. In particular, multi drug-resistant tuberculosis in India will shift from being mainly acquired during treatment to being mainly acquired through primary transmission [18]. The authors project that if current practices continue the incidence of MDR TB could increase substantially from 3.9 cases per 1,00,000 population to 14.1 cases per 1,00,000 population between 2012 & 2032. They estimate that the fraction of MDR TB incidence resulting from primary transmission will rise from 15% to 85% during this time [19]. This study is not alone to find such a substantial transition; Suen and colleagues 42 also projected that by 2035, over 60% of new multidrug-resistant tuberculosis cases will result from transmission rather than be acquired during treatment.

As MDR - TB transmission from an acquired condition to a primarily transmitted disease, the possibility for a sharp upswing in incidence still exists - an upswing that could be prevented with well-crafted public health response. Such an effective response to MDR - TB cannot focus on treating drug susceptible TB alone but must include strong surveillance systems, DST for all patients with TB, rapid linkage to effective treatment and patient centered care throughout the treatment course [19].

The present study was conducted on a random group of Pulmonary and Extra- Pulmonary Tuberculosis patients irrespective of their smear or culture status and not a stratified group of culture positive samples and reflect the burden of MDR-TB in random samples of newly diagnosed patients having clinico-radiological evidence of TB. Hence the results obtained thereof are of much greater magnitude.

Conflicts of interest - The authors have none to declare.

CONCLUSION -

The high proportion of primary drug resistance tuberculosis reported in our study may be attributed to the fact that all patients suspected to have DR - TB were subjected to Gene X-pert or AFB culture unlike the routine practice where only a small proportion of adult patients diagnosed as new TB cases are subjected to these tests. The high proportion of Primary MDR-TB found in our study compels us to suggest that modalities to diagnose primary drug resistance tuberculosis should be made available to all newly diagnosed TB patients presenting with clinico-radiological evidence of tuberculosis, irrespective of HIV status in order to enable detection of primary drug resistance tuberculosis at the onset and prevent the spread of primary drug resistance tuberculosis in the community.

It is worthwhile to subject all patients to Gene X-pert and / or culture and drug sensitivity for effectively controlling the spread of primary drug resistance tuberculosis in the country.

Abbreviations -
1. MDR - Multi Drug Resistance.
2. TB - Tuberculosis.
3. WHO - World Health Organization.
4. XDR - Extensively Drug Resistant.
5. AFB - Acid Fast Bacilli.
6. SDG - Sustainable Development Goals.
7. RNTCP - Revised National Tuberculosis Program.
8. ZNCF-Ziehl Neelsen Carbol Fuchsin
9. DST - Drug Sensitivity Testing

REFERENCES -
1. TB India 2016 Revised National TB Control Programme Annual Status Report, New Delhi, 2016 www.tbcindia.nic.in/
2. WHO media center Tuberculosis Fact Sheet Reviewed March 2017.
3. The WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance - Anti-tuberculosis Drug Resistance in the World. Report no. 2: Prevalence and Trends - WHO/CDS/TB/2000.278
4. RNTCP National Strategic Plan 2012.
5. WHO Global Tuberculosis Report 2016.
6. Tuberculosis control in the South-East Asia Region Annual TB report WHO.
7. TB INDIA 2017 RNTCP Annual Status Report 2017.
8. Epidemiology of Primary Multidrug-Resistant Tuberculosis, Vladimir Region, Russia Julia V. Ershova, Grigory V. Volchenkov, Dorothy A. Kaminski, Tatiana R. Somova, Tatiana A. Kuznetsova, Natalia V. Kaunetis, J. Peter

Cegielski, and Ekaterina V. Kurbatova - Emerg Infect Dis. 2015 Nov; 21(11): 2048– 2051.doi: 10.3201/eid2111.150813

9. Primary Multidrug Resistant Tuberculosis and Utility of Line Probe Assay for Its Detection in Smear-Positive Sputum Samples in a Tertiary Care Hospital in South India - Fahmiya Leena Yacoob, Beena Philomina Jose, Sarada Devi Karunakaran Lelitha, and Sreelatha Sreenivasan -Journal of Pathogens Volume 2016 (2016),Article ID 6235618, 8 pages http://dx.doi.org/10.1155/ 2016/6235618.

10. Primary and secondary anti-tuberculosis drug resistance in Hitossa District of Arsi Zone, Oromia Regional State, Central Ethiopia Shallo Daba Hamusse,Dejene Teshome, Mohammed Suaudi Hussen, Meaza Demissie, and Bernt LindtjørnBMC Public Health. 2016; 16: 593. Published online 2016 Jul 18. doi: 10.1186/s12889- 016-3210-y.

11. WHO Global Tuberculosis Report 2016 - Countries are listed in descending order of the size of their gap.

12. Reichman LB. Unsexy tuberculosis. Lancet 2009;373:28.

13. Nodieva A, Jansone I, Broka L, Pole I, Skenders G, Baumanis V. Recent nosocomial transmission and genotypes of multidrug-resistant Mycobacterium tuberculosis. Int J Tuberc Lung Dis 2010;14:427-33.

14. World Health Organization. Multidrug and extensively drug-resistant TB (M/XDR-TB):2010 global report on surveillance and response 2010. (Accessed August16, 2010,at http://whqlibdoc.who .int/publications/ 2010/ 9789241599191_eng .pdf.)

15. Chan ED, Iseman MD. Multidrug-resistant and extensively drug-resistant tuberculosis: a review. Curr Opin Infect Dis, 2008; 21, 587-95.

16. Faustini A, Hall AJ, Perucci CA. Risk factors for multidrug resistant tuberculosis in Europe: a systematic review. Thorax, 2006; 61, 158-63.

17. Prevalence and Risk Factors of Primary Drug-Resistant Tuberculosis in China - WANG Sheng Fen, ZHOU Yang, PANG Yu, ZHENG Hui Wen, and ZHAO Yan Lin *National Center for Tuberculosis Control and Prevention, Chinese Center for Disease Control and Prevention,Beijing 102206, China.* Biomed Environ Sci, 2016;29(2):91- 98.

18. Emergence of drug resistance in patients with tuberculosis cared for by the Indian health-care system: a dynamic modelling study *Stephanie Law,Amy S Piatek, Cheri Vincent, Olivia Oxlade*, Dick Menzies* - Lancet Public Health* 2017; 2: e47–55 Published Online December 18, 2016 http://dx.doi. org/10. 1016/S2468- 2667(16)30035-4.

19. Multidrug-resistant tuberculosis in India: looking back, thinking ahead Anthony T Fojo David W Dowdy The Lancet Public Health Volume 2, No. 1, e8–e9, January 2017.