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Review Article

Drug Resistant Tuberculosis; Threats, Challenges and Control Strategies in India

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Abstract

Emerging cases of multi drug resistant tuberculosis and extensively drug resistant TB cases pose serious threat to TB control efforts. The systematic review of burden of drug resistant tuberculosis, challenges regarding diagnosis and treatment is presented in this article. In India prevalence of acquired drug resistance is comparatively more than primary drug resistance. The diagnosis of XDR-TB has enormous implications both for the individual and the community. The choice of anti-TB drugs is limited and the ones available are too expensive and too reactogenic.Treatment outcome is mostly disappointing and case-fatality rate is very high in drug resistant truberculosis.

Therefore prompt adherence to DOTS regime, ensuring nationwide access to dignostic and treatment facilities under RNTCP, integrated TB control activities by private and public sector, political commitment ,promoting research and development of national guidelines and policies will definitely help to combat manmade disaster of drug resistant tuberculosis.

Keywords: Drug Resistant Tuberculosis; Challenges; Control.

Introduction

Tuberculosis (TB) remains a major global health problem. India is highest TB burden country in terms of absolute number of incident cases that occur each year. As with all infectious diseases, the more severe the drug-resistance profile, the more difficult it becomes to successfully treat the patient. Multi drug-resistant tuberculosis (MDR-TB) is among the most worrisome elements of the pandemic of antibiotic resistance because TB patients that fail treatment have a high risk of death [1-4]. Extensively drug resistant (XDR-TB) is a severe and serious form of MDR-TB, which responds very poorly to MDR TB treatment. Emerging cases of multi drug resistant tuberculosis and extensively drug resistant TB cases pose serious threat to TB control efforts.

Definitions-Multi drug-resistant tuberculosis (MDR-TB) is defined as a disease due Mycobacterium tuberculosis that is resistant to isoniazide and rifampicin. The term 'extensively drug-resistant tuberculosis' XDR-TB is defined as resistance to at least Isoniazid and Rifampicin (i.e. MDR-TB) plus resistance to any of the fluoroquinolones and any one of the second-line injectable drugs(amikacin, kanamycin, or capreomycin). The term was coined in 2006 by scientists of the Centers for Disease Control and Prevention (CDC), USA [5].

Methodology

The current study is a systematic review of published English-language literature on epidemiology, diagnosis, treatment approaches and outcomes of drug resistant tuberculosis .

Using Pubmed and google databases, articles published in peer-reviewed journals and other authentic literature were searched for terms describing *M. tuberculosis,* drug resistance. Potentially relevant articles were retrieved and each study included was systematically reviewed.

Burden of MDR and XDR TB

In world MDR-TB and XDR TB-Various surveys of drug resistant TB conducted in the world clearly indicate rising trend in the prevalence from 1.1% (1999-2002) to 3.5% (2014)for primary drug resistance and from 7% to 20% for acquired drug resistance [6-9].

Globally, an estimated 3.5% (95% CI, 2.2–4.7) of new cases and 20.5% (95% CI, 13.6–27.5) of previously treated cases had MDR-TB. In 2013, there were an estimated 480,000 (range: 350,000–610,000) new cases of MDR-TB worldwide, and approximately 210,000 (range: 130,000–290,000) deaths from MDR-TB. Drug resistance surveillance data show that an estimated 480 000 people developed MDR-TB in 2013 and 210 000 people died. Extensively drug-resistant TB (XDR-TB) has been reported by 100 countries in 2013 [10].

In India, the prevalence of MDR among new cases has varied between 0.5% to 5% and the primary MDR has remained more or less constant over the years. The acquired drug resistance varied from 25% to 69% in India [6-17].

Table 1: Prevalence of MDR TB in India

Year	Prevalence of primary drug resistance	Prevalence of acquired drug resistance
1999-2002	0.5%	25%
2002	2.8%	69%
2004	2.4%	2.2%
2005	0.7%	17.2%
2008	13.2%	25.5%
2009	2.4%	17.4%
2012	2.1%	15%
2013	2.1%	15%
2014	2.2%	15%

Though these prevalence figures are small in terms of percentages and proportions these rate translates into large absolute numbers [18].

WHO has recognized 58 countries in terms of both the burden and the geographic spread of XDR TB and India is one of those countries [19]. XDR TB has been reported in India by isolated studies with non representative and highly selected samples. In a review of 16 publications on XDR TB cases, a total of 598 cases of XDR-TB have been documented. These reports have originated from 10 tertiary care centres in nine cities, distributed widely in the country. Therefore, the data have no representative value for epidemiological assessment [20,23].

Threats

The diagnosis of XDR-TB has enormous implications both for the individual and the community. The choice of anti-TB drugs is limited and the ones available are too expensive and too reactogenic. Treatment outcome is mostly disappointing and case-fatality rate is very high [24].

Challenges in Diagnosis and Treatment

(1) Although clinical treatment failure is indicative of drug resistance, the diagnosis of MDR-TB and XDR-TB requires the isolation of bacterium and antimicrobial drug susceptibility testing (DST). Therefore, the probability and sensitivity of XDR-TB case-detection in a community are dependent on the coverage and quality of microbiological support services for the diagnosis of MDR TB and XDR TB. Many laboratories with culture facilities for /M. tuberculosis/ may not conduct DST even for first line anti-TB drugs to diagnose MDR-TB. When MDR organisms are detected, DST for second line drugs is unlikely to be conducted, being cumbersome and expensive. (2) Insufficient public sector MDR and XDR TB diagnosis and treatment services-Public sector option for free diagnosis and treatment of MDR TB become available since past few years only (3) Delay in confirmation of diagnosis-Average time taken from identification as MDR TB suspects to DST confirmation report is 45.49 days and this large gap increases transmission and amplifies the magnitude of MDR TB [25]. (4) Poor quality of TB and MDR TB laboratory diagnosis in the private sector-TB is often diagnosed with serology, which frequently mis-diagnoses TB. Recently the use of TB serological testing is banned in India [26]. Drug-susceptibility testing from very few private laboratories has been subject to accreditation of quality. (5) Under reporting-Patients properly diagnosed with TB and MDR TB in private laboratories are not notified to public health authorities, who would be able to take actions to confirm diagnoses, offer supportive services, and offer free treatment to patients from public sources or at least supervise the quality of care in the private sector. (6) Irrational use of Anti-TB drugs - Widespread irrational and irresponsible use and prescriptions, as with all schedule H drugs, provision without prescription is widespread and pharmacists are not required to maintain records of provision that could be used to identify patients with possible TB or MDR TB. Furthermore, second-line anti-TB drugs are widely available in the private sector and used inappropriately, even in drug sensitive TB where such drugs are not required [27]. (7) Lack of valid ,sensitive epidemiological data regarding magnitude of MDR TB and XDR TB. (8) Outcome related challenge -As per recent individual patient data , 48%MDR TB and only one third XDR TB cases has successful outcome [28]. (9) Program related challenge-Drop outs and non traceable patients. (10)

Treatment is expensive and requires 24-30 months for completion [29].

Control Strategies

(1) MDR Prevention through sustained high-quality DOTS implementation. The implementation of a good quality DOTS programme will prevent the emergence of MDR and XDR-TB in the community

(2) Rapid diagnostic tests-Conventional PCR based Line Probe assay and GeneXpert tests endorsed by RNTCP should be widely available.[30]

(3) Strengthening of laboratory services for adequate and timely diagnosis. As of January 2012, diagnosis of XDR TB can only be confirmed at 3 laboratories in India, which are quality-assured for second-line anti-TB drug susceptibility testing of flouroquinolones and injectables. These are the National Reference Laboratories (NRL) of TRC / NIRT Chennai, NTI Bangalore and LRS Institute, New Delhi.Urgent development of national policy and guidelines and innovative design for early diagnosis and case management of XDR-TB.

(4) A national registry of XDR-TB will allow every institution to report cases as soon as they are detected.

(5) The bacilli isolated from each case should be collected and verified in a reference laboratory. Therefore, a number of reference laboratories should be established and networked so that the facility is readily accessible. For patients in whom drug resistance is suspected, diagnosis of MDR-TB should be done through culture and drug susceptibility testing from a quality-assured laboratory.

(6) All relevant investigations to be performed prior to treatment initiation. Preferably the standardized regimen as recommended in the national DOTS-Plus guidelines should be used. If results of second line DST from an accredited laboratory are available, an individualized regimen may be used in such patients after obtaining a detailed history of previous anti-TB treatment [31].

(7) While on treatment, precautions necessary to prevent transmission to members of family and to healthcare workers in contact should be applied.

(8) There is also an urgent need for effective infection-control measures within clinics and hospitals. This must be implemented in every hospital co-ordinated by hospital infection control committees.

(9) Integration of MDR and XDR TB activities with general TB control activities.10) Surveillance of MDR and XDR TB , development and implementation of sound TB control policies [32].

(11) In order to inhibit the development of MDR and XDR-TB, better diagnostic algorithm needs to bedesigned and popularized [33-34].

(12) Scaling up of the DOTS Plus program now known as programmatic management of drug resistant tuberculosis [35].

(13) Addressing XDR-TB in India will be a formidable challenge. The strategy of RNTCP has been to minimize the development of MDR-TB by standardized drug regimens and consequently reduce the emergence of XDR bacilli. The target is to detect and treat at least 30,000 cases of MDR-TB annually, free of charge, from 2012-2013 onwards [36].

(14) Regulation of private sector-Unless TB treatment in private sector is effectively regulated, the problems of MDR- and XDR-TB will remain largely unrecognized.

Conclusion

Drug resistant tuberculosis is an enmerging man-made threat globaly and in India.

Lack of access to rapid and quality dignostic services, expensive and cumbersome treatment, treatment drop outs and outcome failures are the challanges which need to be faced. Its emergence can be prevented by prompt diagnosis and effective use of first line drugs in every new patient. Laboratory drug-susceptibility testing (DST) capacity and access to rapid diagnostics need to improved. Programmatic management of M / XDR-TB must be scaled up as per target set by global plan. Proper use of second-line drugs must be ensured to cure existing MDR-TB, to reduce its transmission and to prevent XDR-TB. Effective implementation of RNTCP, regulation and involevement of private sector in TB control activities, promoting research and surveliance activities, political commitment are the mainstays to prevent and control drug resistant tuberculosis.

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