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Original Article

Multi-drug Resistant Tuberculosis in Rajshahi District

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Abstract

Multidrug-resistant tuberculosis (MDR TB) is a form of tuberculosis that is resistant to at least INH and rifampicin. Total 4390 new patients with sputum smear positive pulmonary tuberculosis were enrolled in this study and treated with 2HRZE /6HT or HE. 3908 patients were cured and 482 patients had to undergo retreatment because of relapse or treatment failure. Retreatment was done with 2HRZES/1HRZE/5$H_3R_3E_3$. Directly observed therapy was employed to treat all the cases. 18 patients remained sputum smear positive after eight months of treatment. So, the percentage of MDR TB in total study population was observed to be 0.4%.And the percentage of MDR TB among retreatment cases were 3.7%.

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Introduction

The multidrug-resistant TB (MDR-TB) that now threatens global TB control programs is conventionally defined as resistance to at least isoniazid and rifampicin.[1] MDR is the most severe form of bacterial resistance. A patient can develop MDR TB in two ways; he /she may be primarily infected with multidrug resistant bacilli from another patient which is known as primary drug resistance or he/she can become multi drug resistant during the course of treatment, known as acquired drug resistance. MDR tuberculosis is mostly acquired. Before diagnosing primary drug resistance, one must be sure that the patient did not receive any anti-tuberculous drugs. Acquired drug resistance is entirely a man made phenomenon. It can occur because of inadequate dosing, incorrect combination of drugs in a regimen, incomplete duration of treatment, irregular therapy etc. It can also be said that MDR TB is the result of faults at different level, faults of patients, faults of doctors and the faults of policy makers. Improper treatment allows individual TB bacilli that have natural resistance to a drug to multiply. Eventually the majority of bacilli in the body are resistant. MDR TB should be suspected if the patient has persistently positive sputum smear, radiological deterioration, or clinical deterioration despite adequate treatment.

One of the major problems in managing MDR TB is that culture sensitivity test is not widely available and test is time consuming. Drug susceptibility can be done using Lowenstein Jensen media (requires four to six weeks), using semisynthetic medium: Middlebrook 7H10, 7H11 by proportion method (require about 3 weeks), Radiometric testing using BACTEC (requires 1-3 weeks) or by Polymerase chain reaction, Luciferase reporter phase etc.

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The resistance of certain M. tuberculosis strains to antituberculosis drugs is not a new phenomenon and, in fact, was noted when streptomycin was first used as monotherapy for tuberculosis, in the 1940s.[2] The rate of spontaneous mutation resulting in resistance to streptomycin (and other drugs) is high enough so that a single drug cannot eradicate all M. tuberculosis organisms in persons with the disease, and over time, resistant organisms will predominate.

Fortunately, the development of multidrug treatment regimens in the 1950s offered a way to overcome the development of resistance, because the rate of spontaneous mutations that result in resistance to two or more drugs is low.[3] From the 1950s through the 1980s; however, the frequency of the transmission of drug-resistant organisms was thought to be low. Reports of outbreaks of drug-resistant tuberculosis were rare and virtually always deemed worthy of publication.[3] In recent years, the situation has changed considerably. From 1990 through 1997, many outbreaks of multidrug-resistant tuberculosis have been reported to the Centers for Disease Control and Prevention.[5,6] In the early outbreaks, the failure to recognize multidrug-resistance patterns rapidly was associated with high mortality rates. Spread was caused by delayed consideration and recognition of multidrug-resistant tuberculosis, delayed initiation of isolation precautions, inadequate ventilation, and lapses in maintaining isolation, and inadequate precautions during cough-inducing procedures.

The World Health Organization estimates that up to 50 million persons worldwide may be infected with drug resistant strains of TB. Also, 300,000 new cases of MDR-TB are diagnosed around the world each year and 79 percent of the MDR-TB cases now show resistance to three or more drugs.[7] MDR-TB has been a particular concern among HIV-infected persons. Immunosuppressed individuals are susceptible not only to acquiring MDR-TB but also to rapid disease progression, which may result in rapid transmission of the disease to other immunosuppressed patients.

MDR-TB is more difficult to treat than drug-susceptible strains of TB. The success of treatment depends upon how quickly a case of TB is identified as drug resistant and whether an effective drug therapy is available. The second-line drugs used in cases of MDR-TB are often less effective and more likely to cause side effects.[8] Tests to determine the resistance of a particular strain to various drugs usually takes several weeks to complete. During the delay the patient may be treated with a drug regimen that is ineffective. Once a strain's drug resistance is known, an effective drug regimen must be identified and begun. Some strains of MDR-TB are resistant to seven or more drugs, making the identification of effective drugs difficult. Treatment for MDR-TB involves drug therapy over many months or years. Despite the longer course of treatment, the cure rate decreases from over 90 percent for nonresistant strains of TB to 50 percent or less for MDR-TB.[9] Drugs used to treat MDR TB is not easily available and are costly. So, prevention of MDR TB is a much better option than to treat it. Because it is difficult for some people to successfully complete their tuberculosis treatment, several innovations have been developed. One of these is the use of incentives and enablers, which may be transportation, tokens or food coupons that are given to patients each time they appear at the clinic or doctor's office for treatment. Incentives and enablers are combined with the use of Directly Observed Treatment Short course (DOTS) strategy. DOTS is a system of treatment in which the patient is administered his or her medication by a nurse or health worker and observed taking the medication. In our country, DOTS is being implemented throughout the country. FDA has approved fixed dose combination therapy for the treatment of tuberculosis. This reduces the number of pills a patient has to take each day and makes it impossible for the patient to take only one of the three medications, a common path to the development of MDR-TB.

Materials and methods

This was a prospective type of study done in nine Upazilla health complexes of Rajshahi district and

DOTS corner of Rajshahi medical college hospital. Study period was January 1998 to December 2004. Total 4390 new patients with sputum smear positive pulmonary tuberculosis were enrolled in this study. They were treated with 2HRZE /6HT or HE (isoniazid, rifampicin, pyrazinamide and ethambutol for two months followed by isoniazid and thiacetazone or isoniazid and ethambutol for six months). 3908 patients were cured and 482 patients had to undergo retreatment because of relapse or treatment failure. Retreatment was done with category 2 regimen, i.e. $2HRZES/1HRZE/5H_3R_3E_3$ (isoniazid, rifampicin, pyrazinamide, ethambutol and injection Streptomycin for two months, followed by isoniazid, rifampicin, pyrazinamide, ethambutol for one month and then isoniazid, rifampicin and ethambutol thrice weekly; at least one day apart, for five months). Directly observed therapy was employed to treat all the cases. 18 patients remained sputum smear positive after eight months of treatment with category 2 regimen. From these patients sputum was obtained and sent to Shyamoli TB control center, Dhaka and also in Damien foundation, Belgium for culture and sensitivity test.

Results

All the 18 patients who remain smear positive at the end of category 2 treatment found to have MDR tuberculosis. So, the percentage of MDR TB in total study population was observed to be 0.4%.And the percentage of MDR TB among retreatment cases were 3.7%. Yearly occurrence of MDR TB in Rajshahi district ranged from 1 to 5. Out of 18 patients with MDR TB, 12 patients (66.66%) were resistant to INH, rifampicin, streptomycin and ethambutol; 3 patients (16.66%) were resistant to INH, rifampicin, and ethambutol; 2 patients (11.11%) were resistant to INH, and rifampicin; 1 patient (5.55%) was resistant to INH, rifampicin, and streptomycin. All the 18 cases were found to be sensitive to pyrazinamide, prothionamide, kanamycin, and ofloxacin.

Table 1: Incidence of MDR TB in total study population

Total patients	MDR TB	Percentage
4390	18	0.41%

Table 2: Incidence of MDR TB among retreatment cases

Retreatment cases	MDR TB	Percentage
482	18	3.73%

Table 3: Year wise distribution of MDR TB (N=18)

year	Number of MDR TB patients
1998	1
1999	2
2000	4
2001	5
2002	2
2003	3
2004	1

Table 4: Drug resistance pattern observed in our study (n=18)]

Resistance to	Number of patients	Percentage
INH, rifampicin, streptomycin, and ethambutol	12	66.66%
INH, rifampicin, and ethambutol	3	16.66%
INH, and rifampicin	2	11.11%
INH, rifampicin, and treptomycin	1	5.55%

Discussion

Multidrug-resistant tuberculosis has emerged as a possible threat to global tuberculosis control efforts in recent years. It is a challenge not only from a public health point of view but also in the context of global economy, especially in the absence of treatment for MDR-TB at national-level programs in developing countries.Because of the emergence of MDR organisms, determination

of the drug susceptibility panel of an isolate is important so that appropriate treatment can be ensured. Numerous chromosomal mutations are associated with drug resistance. Genotypic methods now being employed to identify these mutations including DNA sequencing, solid phase hybridization, and PCR–single-strand combination polymorphism analysis. Mutations of the catalase peroxidase gene ***katG***, the ***inhA*** gene involved in fatty acid biosynthesis, the ***ahpc*** gene, and the ***oxyR*** gene have been identified as major determinants for isoniazid (INH) resist. Resistance to rifampin is determined by mutations in the ***rpoB*** gene encoding the beta subunit of the RNA polymerase. Phenotypic susceptibility assays, which remain experimental, employ mycobacteriophages to type the mycobacteria grown in the presence of antituberculous agents.[10]

Fortunately, there is a way to prevent drug resistance: ensure that patients with tuberculosis throughout the world have access to adequate tuberculosis control programs. Such programs can ensure that patients adhere to their treatment regimens and that the regimens are the best available. The world community, and especially developed countries, have a responsibility to support the World Health Organization and developing countries in setting up and maintaining adequate tuberculosis control programs. Resources are also needed for the treatment of persons with multidrug-resistant tuberculosis. Concern about the increasing prevalence of potentially incurable forms of multidrug-resistant tuberculosis may provide a unique opportunity to overcome apathy and mobilize the much-needed societal commitment to effective tuberculosis control. A much greater commitment will be required if we are to ward off what could become a global health disaster. A serious research effort to develop effective drugs or vaccines targeting persistent or dormant Mycobacterium tuberculosis infection. With such interventions, we might someday be able to prevent reactivation in those who are tuberculin-positive (about a third of the people on the globe). However, 95 percent of cases of tuberculosis occur in poor residents of developing countries, and there are few market incentives to develop such drugs. It is encouraging that new public–private collaborations — such as the Global Alliance for tuberculosis Drug Development to develop new anti- tuberculosis drugs and the Global Drug Fund to purchase and distribute existing drugs — have been created. In June 1998, the U.S. Food and Drug Administration approved the first new drug for pulmonary tuberculosis in 25 years. The drug, rifapentine, has been approved for use with other drugs to fight TB. One potential advantage of rifapentine is that it can be taken less often in the final four months of treatment -- once a week compared with twice a week for the standard regimen.

In our study, we have observed that incidence of MDR tuberculosis in Rajshahi district of Bangladesh is relatively low (0.41%). Actually, it is lower than that is observed in USA. According to CDC, 1.3% of US tuberculosis cases have MDR TB.[9] The Global Project on Anti-Tuberculosis Drug Resistance Surveillance, Report no. 2, revealed that the median prevalence of MDR in strains isolated from new cases (primary drug resistance) was only 1% (range 0-14.1%), whereas the median prevalence in previously treated cases (acquired drug resistance) was 9.3% (range 0-48.2%).[11] Russia seems to have a higher prevalence of MDR TB than us. In Russia, between 1997 and 1999, the prevalence of MDR-TB rose from 6% to 13% in all civilians with TB, whereas among chronic cases the prevalence of MDR-TB was over 60%.[12] Studies undertaken in Tamilnadu state by the TB Research Center during the period 1997-1999 revealed a prevalence of MDR-TB of 3%.[13] So, it seems that, TB control program of Rajshahi district of Bangladesh is highly efficient and satisfactory.

Conclusion

MDR TB is still not a great threat to our community. It is due to successful implementation of DOTS program throughout the country and good cooperation and collaboration between government and private sector including the NGO’s dedicated to fight tuberculosis.

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