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# Multi-Drug Resistant Tuberculosis - Experiences of Treatment at IDC&H

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**Abstract**

*Background -Tuberculosis is the world's most important communicable disease with an extremely deadly form called "multi drug resistant tuberculosis (MDR-TB)" which is defined as resistance to both isoniazid and rifampicin. The Institute of Diseases of the Chest and Hospital (IDC&H) is the only tertiary referral center for complicated chest and TB patients in Bangladesh. It caters to a large number of complicated TB cases, including MDR-TB cases. Methods- Case records of 41 patients admitted under the Department of Medicine in IDCH presently undergoing or having completed treatment for MDR-TB were reviewed. Patients admitted from March 1999 onwards and those who have completed the initial intensive phase of treatment within June 2001 were included. MDR-TB cases were diagnosed on the basis of culture and susceptibility results (n=14) or as "Clinical MDR-TB" (n=27) i.e. chronic patients who were sputum smear positive after completion of 5 months of fully supervised WHO re-treatment regimen i.e. Category II (2 SRHEZ, 1 RHEZ, 5RHE). The MDR - TB treatment regimen employed consisted of an intensive phase of 3 months duration using Kanamycin, Ethionamide, Pyrazinamide, Ofloxacin and Ethambutol followed by 18 months of Ethionamide, Ofloxacin and Ethambutol. In addition to routine clinical evaluation, 3 consecutive sputum samples were examined on a monthly basis beginning at the end of the first month. Results- There were 32 men and 9 women with mean age of 27.8 years (range 16-42 yrs). A quarter of the patients have completed treatment, half are improving i.e. have converted to smear negative and are continuing treatment, five have died and four have been labeled as "failure" i.e. they are smear positive after 5 months of treatment. One patient who had failed to convert at 3 months underwent pneumonectomy and ultimately improved. The majority of patients (59%- 19/32) converted within 1 month followed by 4/32 in 2 months. Gastrointestinal symptoms led the list of side effects affecting more than three-quarters of the patients. Conclusions- Treatment of MDR-TB with a 21-month regimen under full supervision in a specialized center can provide satisfactory results. Surgery is an useful adjunct to medical treatment. Comprehensive measures should be focused on the prevention of MDR-TB. In failure cases at any stage, a single drug should never be added. Indiscriminate use of fluoroquinolones viz. Ciprofloxacin and Ofloxacin should be discouraged.*

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## Introduction

Tuberculosis is the world's most important communicable disease[1]. Although TB cases declined in the 70s leading to a false sense of relief, the world has witnessed an alarming rise of TB in the last two decades[2,3]. In 1993, WHO declared TB as a global emergency and recommended DOTS as the appropriate strategy for its effective control[4]. Unfortunately, TB has not only struck back, it has returned with vengeance in a deadly form called "multi drug resistant tuberculosis TB" which is defined as a case of tuberculosis caused by a strain of M. tuberculosis that is resistant to both isoniazid and rifampicin, the two main anti-tuberculosis drugs, with or without resistance to other drugs[5]. An isolate of M. tuberculosis is considered resistant to a drug if the number of colonies on the drug-containing medium is >1 % of the number of colonies on the drug-free plate[6].

According to a survey conducted in 35 countries, the overall prevalence of MDR-TB was 2.2% of TB cases (range 0-22.1%)[7]. In Bangladesh, limited studies have reported the prevalence of primary (patients without history of anti-TB drug intake) and secondary/acquired (patients with history of anti-TB drug intake) resistance to be 4.9%[8] and 5.6%[9], respectively. MDR-TB is a catastrophic man made phenomenon due to ineffective administration of effective drugs[10]. We have reviewed the factors contributing to the development of MDR-TB previously[11]. Successful management of this deadly disease is a formidable challenge to the medical profession due to the following problems-

1. Requires second line drugs, which are very toxic, very expensive and not easily available.
2. Duration of therapy is very long (minimum 21 months)
3. Hospitalization is mandatory:
   a) For strict supervision of treatment. (Intensive phase at least)
   b) For prevention of transmission
4. Easily transmitted to health care workers.
5. High risk of nosocomial transmission.
6. High mortality in comparison to susceptible TB.
7. Period of infectivity is longer- a threat to effective control.
8. Diagnosis of drug resistance is expensive, cumbersome and time-consuming.
9. Chances of failure are 83 times more (11.6% vs. 0.15%)[12]
10. Chances of relapse is double[13].

The Institute of Diseases of the Chest and Hospital (IDC&H) is the only tertiary referral center for complicated chest and TB patients in Bangladesh. It caters to a large number of complicated TB cases, including MDR-TB cases. In accordance with WHO recommendations for mandatory admission and fully supervised treatment of MDR-TB patients[10], patients remain admitted in IDC&H for the whole duration of their treatment.

Heretofore, 41 patients have received treatment for MDR-TB at IDC&H. In this paper, we describe our experiences in the management of these patients.

## Methods

Case records of 41 patients admitted under the six units of the Department of Medicine in IDC&H who are presently undergoing or have completed treatment for MDR-TB was reviewed. Patients admitted from March 1999 onwards and those who have completed the initial intensive phase of treatment within June 2001 were included.

*Case definition-*

MDR-TB cases were diagnosed on the basis of

1) Culture and susceptibility results (n=14) (Table 1)
2) "Clinical MDR-TB" (n=27)

In chronic patients who were sputum smear positive after completion of 5 months of fully, supervised WHO re-treatment regimen i.e. Category II (2 SRHEZ, 1 RHEZ, 5RHE)[14]. In our cases, owing to persistent smear positivity, we administered streptomycin for 3 months (3SRHEZ, 2RHE).

*Treatment-*

Drugs and their doses used for the treatment of the TB patients, including MDR-TB are tabulated in Table-I. The regimen employed for our patients was

| Phase | Duration | Drugs |
|---|---|---|
| Intensive | 3 months | K Z Eth O E |
| Continuation | 18 months | Eth O E |

Abbreviation : K- Kanamycin, Z-Pyrazinamide

Eth- Ethionamide, O- Ofloxacin

E- Ethambutol

*Follow-up :*

In addition to routine clinical evaluation, 3 consecutive sputum samples were examined on a monthly basis beginning at the end of the first month. Sputum examination was continued for patients with persistently positive samples. In patients showing conversion, samples were repeated at quarterly intervals.

## Results

There were 32 men and 9 women in our study. The mean age was 27.8 years (range 16-42 yrs). The overall treatment outcome for these patients is summarized in Table 3. A quarter of the patients have completed treatment, half are improving i.e. have converted to smear negative and are continuing treatment. Unfortunately, five have died and four have been labeled as "failure" i.e. they remain smear positive after 5 months of treatment. One patient who had failed to convert at 3 months underwent pneumonectomy and ultimately completed treatment. The duration of treatment till sputum conversion is illustrated in Figure-1. The majority of patients (59%- 19/32) converted within 1 month followed by 4/32 in 2 months. The frequency of side-effects of drugs encountered during treatment have been tabulated in Table 4. Gastrointestinal symptoms led the list affecting more than three-quarters of the patients.

**Table-I**

*Results of culture and susceptibility*

| Drug | Resistant | Sensitive |
|---|---|---|
| Rifampicin | 14 (100%) | 0 |
| INH | 14 (100%) | 0 |
| Ethambutol | 2 (14%) | 12(86%) |
| Streptomycin | 3 (21 %) | 11 (79%) |

**Table-II**

*Drugs used in TB, particularly MDR-TB with doses*

| Drugs | Abbreviation | Dose |
|---|---|---|
| Inj. Streptomycin | (S) | 15mg/kg |
| Inj Kanamycin | (K) | 15mg/kg |
| Tab. Ethionamide | (Eth) | <50 kg-500 mg/day |
| Tab. Prothionamide | | >50 kg-750 mg/day |
| Tab. Ofloxacin | (O) | 800 mg daily |
| Tab. Ethambutol | (E) | 15-25 mg/kg |
| Tab. Pyrazinamide | (Z) | 35 mg/kg |
| Cap. Rifampicin | (R) | 10 mg/ kg |
| Tab. INH | (H) | 5 mg/kg |

**Table-III**

*Treatment Outcome*

| Outcome | No. of patients | Percentage |
|---|---|---|
| Completed | 10 | 24.3 |
| Failure | 04 | 9.7 |
| Deaths | 05 | 12.2 |
| Improving | 22 | 53.8 |

**Table-IV**

*Occurrence of side effects*

| Side effect | No. of patients | Percentage |
|---|---|---|
| Heartburn, dyspepsia | 32 | 78% |
| Anorexia | 21 | 51% |
| Vomiting | 15 | 37% |
| Pruritus | 10 | 24% |
| Arthralgia | 8 | 20% |
| Jaundice | 4 | 10% |

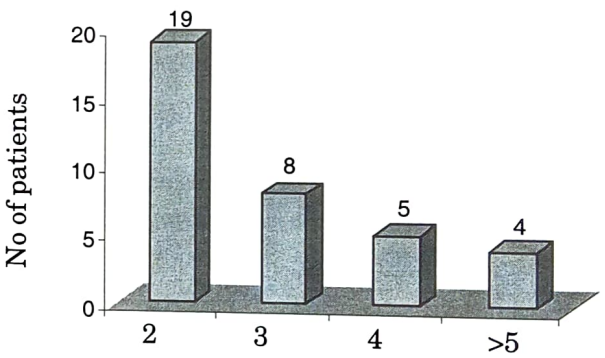


***Fig.-1 :*** *Conversion of Sputum in Relation to duration of treatment*

## Discussion

The majority of our patients were diagnosed on the basis of their failure to respond to supervised Category II (2SRHZE/1 RZHE/5REH). Culture/ susceptibility testing was not possible in all cases due to the dearth of culture facilities in the public sector. The expenses of culture testing in private laboratories were borne by the patients themselves. Fortunately, a tuberculosis culture laboratory has been set up at the Shyamoli national TB control project recently, which hopefully can

provide quit essential diagnostic services. Establishment of a national reference laboratory for tuberculosis, in the near future is imperative. The Damien Foundation (DF) is treating 67 patients diagnosed as MDR-TB patients on the basis of bacteriological or molecular investigations done in Belgium[15].

Drug supply has been an extremely important issue in the management of these patients. Although the IDCH authorities have allowed admission of the patients for the entire duration of their treatment and other drugs, all the second -line drugs (K,Eth,O) had to be procured by the patients through private donation or support from NGOs. The IDCH MSR budget has no provision for second -line anti-tuberculous drugs. An NGO Christian Service International (CSI) has provided drugs for 23 patients-this includes 6 patients who have completed their treatment.

Among our patients, the number of men was more than thrice than that of women which is concordant with a group undergoing treatment under Damien Foundation[15]. In a report from Turkey, the male preponderance was more marked (M:F = 6:1)[16]. The age of our patients represents the most vulnerable age group for TB.

The drug regimen has been established in conformity with basic principles laid down in WHO guidelines[10]. In Bangladesh, the DF has been treating MDR-TB patients with a 21-months regimen divided into three phases (3KCOPHZE/12 OPHZE/ 6EP)[16]. A considerable proportion of patients in our study (53%- 22/41 ) and DF's study (42%- 28/67 )are still undergoing treatment - they have all remained smear negative after conversion. The treatment completion rate and deaths in the 2 studies are somewhat concordant. However, the failure rate is higher in our study (10% vs. 4%). Fifty-nine percent of our patients (19/32) had become smear-negative within 2 months of therapy. This is an optimistic sign by virtue of which the majority of patients will ultimately need a continuation phase, shorter by at least one month.

Interestingly, there were no defaulters in our study whereas DF had 13% these were patients who abandoned treatment due to side effects. The higher number of drugs in the DF study may have contributed to increased occurrence of side effects. Gastrointestinal symptoms were the most common side effect with heartburn leading the list (78%). The symptoms were relatively well managed by giving drugs after meals, and through addition of H2 receptor antagonists and antacids. Easy availability of proton pump inhibitors also facilitated management. Jaundice was an ominous sign, since 75% of patients with jaundice ultimately died.

Surgery has a good role in the management of patients not responding to medical therapy alone. This is more marked in patients with thick walled cavities and localized disease. In our series, a patient with refractory MDR-TB underwent pneumonectomy following which she become smear negative. The patient who underwent surgery was a nurse- an example of nosocomial transmission and a matter of grave concern for all medical professionals. In the Turkish series, 23% patients underwent surgery, whereas in a report from National Jewish Center for Immunology and Respiratory medicine, 85% of patients became negative after surgery[17]. Surgery if indicated should be employed at an early stage- preferably at 3-4 months so that enough time is available for post-operative treatment. According to step-wise logistic regression analysis done by the Turkish group, a successful outcome in the treatment of MDR-TB was independently associated with younger age group and the absence of previous treatment with ofloxacin[17].

The incidence of MDR-TB is a major global problem. Fortunately, an innovative community based treatment approach branded "DOTS-plus" has been developed to combat this menace[18,19]. The WHO is also developing a program for the management of this scourge[20]. This program will focus on the main obstacle i.e. prohibitive costs of second-line drugs, by lowering drug prices.

**Conclusions**

1. All measures should be focused on the prevention of MDR-TB, since it can be a virtual death sentence.
2. All treatment failure/relapse cases should not be labeled as MDR-TB, at the very outset. Rather, physicians should properly employ Category II treatment (fully supervised) before dubbing a patient as MDR-TB. For the purpose of supervision, mandatory

hospitalization for the intensive phase should be practiced.

3. In failure cases at any stage, a single drug should never be added- monotherapy is tantamount to gross negligence.
4. Indiscriminate use of fluoroquinolones viz. Ciprofloxacin and Ofloxacin should be discouraged
5. Treatment of MDR-TB with a 21-month regimen under full supervision in a specialized center can provide satisfactory results.
6. Surgery should be borne in mind as a particularly useful adjunct to medical treatment.

Recommendations for control of MDR-TB in Bangladesh

- Establish national reference laboratory for culture and susceptibility testing
- Carry out drug resistance surveillance studies
- Make second line drugs easily available for specialized centers like IDC&H by
  - procurement of second line drugs
  - applying to the WHO green light committee
- Consider introduction of DOTS-plus
- Ensure closer coordination between NTP, IDC&H, NGOs and practitioners

**For practitioners**

- The knowledge of all consultants, specialists and general practitioners about anti-TB drugs should be updated.
- All doctors should be convinced that simply prescribing drugs for patients is not enough. The ultimate success lies in ensuring compliance in TB patients by explaining the disastrous consequences of noncompliance like MDR-TB. For ensuring compliance, the physicians can nominate a family member as the "DOTS supervisor" for the patient. We should remember that our non-compliant patients shall ultimately become reservoirs of MDR-TB and subsequently may pass it on to our family members and us.

**At social level**

1) Social awareness about the resurgence of TB and its deadly multi drug resistant form should be increased.
2) Elected representatives, government officials and local community leaders should be motivated for this purpose.
3) Remedies should be sought for problems like poverty and social injustice.
4) Formation of TB club for ensuring DOTS.

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