Original Article

Drug resistance to tuberculosis in a tertiary care setting in Karachi

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Abstract

Objective: To evaluate the resistance pattern of tuberculosis cases.

Methods: A descriptive study was done in two out patient referral clinics from January 1999 to March 2003. All TB cases that had cultures positive for mycobacterium tuberculosis were evaluated.

Results: Data from 71 proven culture positive patients was available. Resistance to at least one antituberculous drug was found in 44 (60.5%) cases. Primary, Initial and Secondary Resistance to at least one drug was 7.0%, 21.1% and 32.3% respectively. Out of 7.0% primary resistance cases, there were 5.6% of single drug resistance, 1.4% Multiple Drugs and zero percent of Multi drug Resistance (MDR). Initial resistance cases (out of 21.1%) included 12.6% to single drug, 7% to multiple drugs and 1.4% MDR. Acquired Resistance Cases (out of 32.3%) included 5.6% each to single and multiple drugs and 21% MDR. Single drug resistance (for primary, initial and acquired) showed 14% resistance for Isoniazid, 4.2% for Rifampicin, 2.8% each for Ethambutol and Streptomycin and 1.4% to Pyrazinamide.

Conclusion: In this cohort of patients, Primary resistance to at least one drug was 7.0% and no MDR. Among individual drugs, resistance to Isoniazid was highest (14%) and lowest for Pyrazinamide (1.4%) (JPMA 57:282;2007).

Introduction

Drug Resistant TB was first observed in 1946, subsequent to the first trials of streptomycin for TB treatment.[1] Ever since, drug-resistant TB has been recognized to occur due to various reasons[2-4], foremost being sub optimal TB treatment.[5] Thus most cases of TB are drug susceptible at the time of diagnosis, only becoming drug resistant through sub optimal therapy, although spontaneous mutation may also account for some resistance.[6]

Drug-Resistant TB occurs when drug-resistant bacilli outgrow drug-susceptible bacilli. The drug-resistant organisms are produced by random mutations in the bacterial chromosome which occur spontaneously in wild type strains even before the strains come in contact with the drug.[6]

The importance of culture and sensitivity cannot be over emphasized in our community although it has many problems. Apart from non-producers of sputum and a long wait for the results, they include high cost and lack of reliable and reference laboratories. These are the reasons why cultures are less frequently done in suspected TB cases in Pakistan and hence limited data is available from this part of the world. TB culture is usually advised when physicians suspect drug-resistant TB in the individual.

In developing countries like Pakistan, detection of Pulmonary TB is usually based on sputum smear examination although it has got multiple limitations like unavailability of sputum, low yield as compared to culture and no information on resistance.

Resistance to anti TB drugs varies from country to country and reflects adequacy of TB control in the community. Unfortunately the resistance pattern of tuberculosis in not well studied in our community as evident by paucity of available data. We did this study from out patient urban population to highlight the resistance pattern in the mega city of Karachi.

Materials and Methods

The following terms have been used in this study following accepted nomenclature7:

Drug-Resistant Tuberculosis: Mycobacterium tuberculosis bacilli (MTB) resistant to one or more first line anti tuberculosis drugs. These include Rifampicin (R), Isoniazid (H), Ethambutol (E), Streptomycin (S) and Pyrazinamide (Z).

MDR-TB: MTB bacilli resistant to at least Isoniazid and Rifampicin.

Multiple Drug Resistance: MTB bacilli resistant to any two or more drugs, except the combination of R and H

Primary Drug Resistance: Resistant strain of MTB in a patient with no history of previous anti TB treatment (ATT).

Acquired Drug Resistance: Resistant strain of MTB in a patient who has taken at least one month of anti-TB drugs treatment in the past.

Initial Resistance: Where previous history of ATT is not known or is uncertain.

Data from two out patient tertiary care referral clinics was evaluated; patients whose MTB culture and sensitivity reports were available from January 1999 to March 2003 were included.

The ethical issues in this study were found to be consistent with the protocols adapted elsewhere.[7]

Resistance pattern was categorized according to patient's prior Tuberculosis (TB) history as Primary, Acquired or Initial. Those cases in which a previous TB treatment history was missing were classified as initial resistance; this would include majority of primary resistance cases and some undisclosed acquired resistant cases.

The data was then evaluated as single drug resistance, multiple drug resistance and MDR in all the three above-mentioned categories. We also evaluated our data as over all resistance to one drug, two drugs, three drugs and four drugs.

Seventy one specimens included 66 samples of sputum, 2 pleural fluids and one each of lymph node, urine and muscle biopsy. The culture was done on LJ medium and sensitivity was checked by proportion method.

The statistical analysis was done using Microsoft Excel sheet and frequency of resistance was assessed. The data was tabulated under the headings of Primary, Initial and Acquired drug resistance as mentioned in the results.

Results

Data from 71 proven culture positive patients was available of whom 71% were also sputum smear positive. Twenty nine were females and 42 males. The average age of patients was 44 years (14 to 82) and 64% were married. Regarding occupation, majority were house hold ladies (21%), followed by businessmen (14%). Co morbid illnesses included obstructive lung disease 10 (14%) patients and Diabetes Mellitus 9 patients (12%). Six patients had positive contact history of TB while it was unavailable in the remaining 65.

Of all cases 66 (93%) were suffering from pulmonary TB as confirmed by sputum culture. Among extra pulmonary cases, there were pleural effusion (2 cases), lymph node (1 case), kidney (1 case) and skeletal muscle (1 case).

A definite past history of TB was found in 24 (33.8%) patients; no history of previous TB or taking Antituberculous Therapy (ATT) was found in 15 patients (21.1%); in the remaining 32 patients (45.1%) it was inconclusive.

Resistance to at least one antituberculous drug was found in 44 (60.5%) cases. Primary, Initial and Acquired Resistance to at least one drug was 7.0%, 21.1% and 32.3% respectively. (Table 1)

Table 1. Resistance pattern according to the History of tituberculous Therapy.

	Single drug	Multiple drug	MDR	Total Resistance
Primary Resistance	5.6%	1.4%	None	7.0% (5)
Initial Resistance	12.6%	7.0%	1.4%	21.1% (16)
Acquired Resistance	5.6%	5.6%	21%	32.3% (23)
Total	23.9%	14.08%	22.5%	60.5% (44)

Table 2. Resistance pattern of individual drugs.

Name of Drug	Overall resistance (Single, Multiple, MDR)	Single drug resistance
INH	45%	14%
Rifampicin	30%	4.2%
Ethambutol	11.2%	2.8%
Pyrazinamide	22.5%	1.4%
Streptomycin	18.3%	2.8%

Out of 7.0% primary resistance cases, there were 5.6% to single drug, 1.4% to multiple drugs and none of MDR. Initial and Acquired Resistance Pattern are shown in the Table 1.

Single Drug Resistance (for Primary, Initial and Acquired) showed 14% resistance to INH, 4.2% to Rifampicin, 2.8% each to Ethambutol and Streptomycin and 1.4% to Pyrazinamide. Overall resistance to single drug showed highest resistance to INH (45%). Full details are shown in Table 2.

When we analysed resistance from the aspect of number of drugs, we found that 27 (38%) patients were sensitive to all five primary drugs (including streptomycin), 18 (25%) were resistant to single drug, 14 (20%) to two drugs, 5 (7%) to three drugs and 7 (10%) were resistant to all four primary drugs.

Discussion

Tuberculosis drug resistance has been discussed with variable depth in many studies. In Pakistan very little data is available compared with the burden of the disease. Besides this, there are even fewer studies from the mega city of Karachi.

In Pakistan, cultures are not routinely done on all TB suspects because of the cost and lack of reliable laboratories. Many centres perform cultures only on re-treatment cases i.e. those that relapse after a previous full course of treatment or interrupted treatment, to know the expected resistance in such cases. We could not ascertain the reasons for this selection in our study group although they were not all 'difficult" cases.

We have categorized resistance according to the

previous treatment history available from the records. In our study, the cases in which a previous TB treatment history was missing were classified as initial resistance; this would include majority of primary resistance cases and some undisclosed acquired resistant cases. There are variations of such categorization in different studies and some have included initial resistance within primary.[7,8]

The overall resistance to at least one Anti TB drug was 60%. This may have a selection bias as described above but is reasonably comparable to other local studies giving figures of 76%[9] and 53%.[10]

The highest resistance to a single drug was to INH, 14% as single drug and 45% overall. This is comparable to other local data where INH resistance was 25 to 60%.[9,11-13]

Rifampicin as single drug was resistant in 4% cases and 30% overall. Rifampicin has low primary resistance in local studies[9,10], which also was the case in our study. Some of the local studies show a different pattern of resistance especially for Rifampicin where its resistance was comparable to INH.[11,12] A study from Rawalpindi has shown the resistance with Rifampicin to be even higher than INH.[13]

The incidence of MDR was also comparable to local data where MDR was 24%[9] and 21%[14]; ours being 22.5%. Primary Resistance is expectedly low in majority of studies worldwide. Our figures correlate with both local and international data.[7-10,15]

Acquired Resistance reflects the adequacy of TB control in the country. In Pakistan TB control is still far from being optimal, the acquired resistance of 32% is no surprise. Same is the case with other local[9,11] and international studies.[7,8] It has been shown that the implementation of an effective tuberculosis control program can revert the resistance pattern to a lower point than before.[16]

Our cases were mostly pulmonary, the resistance in extra pulmonary cases is supposed to be low[17] except in a study of 98 cases, which showed around 40% resistance.[18] In this study almost half of the specimens were pus, which may include body fluid from chronic TB sufferers. Global resistance pattern to ATT varies from region to region[7,8] and is expectedly low in non-endemic areas and high in endemic areas. However, facts like the highest resistance with INH and low MDR in primary TB cases, matches with the results of local and international studies.[7,8]

Our study included only those patients whose positive culture and sensitivity reports were available. It may be argued that the true picture of the resistance pattern may only be known if culture is done in all the suspected cases of tuberculosis. But as discussed earlier it is rarely done in Pakistan because of lack of resources on part of the patient and lack of good laboratory facilities on part of the health authorities. It would be a great service if arrangements are made to cut down the cost of culture and sensitivity without affecting the quality.

The resistance especially MDR was high in re-treatment cases, so it can be argued that all the re-treatment cases should have their culture and sensitivity done.

Conclusion

In this cohort of patients, Primary resistance to at least one drug was 7.0% and no MDR. Among individual drugs, resistance to Isoniazid was highest (14%) and lowest for Pyrazinamide (1.4%).

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