March 2008

Primary drug resistance against Mycobacterium tuberculosis in Karachi

Nisar Ahmed Rao
Aga Khan University

Muhammad Irfan
Aga Khan University

Shahid Javed Hussain
Aga Khan University

Original Article

Primary drug resistance against Mycobacterium Tuberculosis in Karachi

Nisar Ahmed Rao, Muhammad Irfan, Shahid Javed Hussain
Department of Medicine, Aga Khan University, Karachi, Pakistan.

Abstract

Objective: To evaluate the primary drug resistance of new culture positive cases of pulmonary tuberculosis in Karachi.

Methods: All new suspected pulmonary tuberculosis patients were recruited initially. They were instructed to produce three-sputum samples for smear examination and on one of the specimen's culture was applied. Bronchoscopy and bronchial wash was done in patients who were not expectorating. Bronchial wash was then applied for both smear and culture for mycobacterium tuberculosis.

Results: Out of 79 cases recruited initially, 52 were able to produce sputum while bronchoscopy was performed in the remaining. AFB direct smear was positive in 32/52 sputum and 12/27 bronchial wash samples. Later, 02 sputums and 04 bronchial washes became culture positive which were initially smear negative. All cultures were of Mycobacterium tuberculosis species. These fifty culture positive cases were then included in the final analysis. Pyrazinamide was the most sensitive drug i.e. 49 isolates (98%). The resistance pattern is as follows: Streptomycin 13(26%), Isoniazid 08 (16%), Ethambutol 08 (16%), Rifampicin 04 (08%) and Pyrazinamide one (02%). Multi-Drug Resistant tuberculosis was observed in 02 (04%) patients.

Conclusion: In this small study, the high prevalence of primary resistance against streptomycin, INH and Ethambutol raises an urgent need of a proper nationwide survey to evaluate the true picture of primary resistance (JPMA 58:122;2008)

Introduction

In Pakistan, tuberculosis constitutes a major public health problem and its incidence is rising due to multi-factorial reasons including poverty, ignorance, over the counter sale of anti-tuberculosis drugs and availability of poor quality medications. Globally Pakistan has been ranked 7th in terms of estimated number of cases by WHO,

with an incidence of 181/100,000 persons.[1]

The data on resistant tuberculosis is sparse from Pakistan and for the successful control of tuberculosis there is a need to have regular surveillance of resistance pattern in the community. The aim of the study was to evaluate the present scenario of primary drug resistance of new cases of pulmonary tuberculosis in Karachi. This study will have an impact on management guidelines.

Patients and Methods

This study was conducted from October 2004 to August 2005 at pulmonary section, Department of Medicine, Aga Khan University Hospital, Karachi. Karachi is the largest metropolis of Pakistan with a population of more than 11 million. Aga Khan Hospital (AKH) is a 600-bedded tertiary care teaching hospital located in Karachi, Pakistan. The hospital and laboratory are accredited with Joint Commission of International Accreditation (JCIA). Laboratory is routinely participating in external quality control surveys with College of American pathologists (CAP) sine 1992. The number of patients seen in Pulmonology outpatient clinics exceeds 14,000 per year.

Cases were enrolled from the pulmonary clinics of Aga Khan University Hospital (AKUH). Majority of the recruited patients were from middle and low socio-economic group. All patients have full access to over the counter sale of anti-TB drugs.

Patients with suspected pulmonary tuberculosis on clinical and radiological grounds were recruited initially. In this study none of the recruited patients purchased the ATT (Anti-tuberculosis treatment) over the counter, which was specifically inquired, and patients with past history of ATT were excluded. Assurance was made that they were new cases and had never received anti-tuberculosis treatment in the past.

The recruited subjects were instructed to produce three-sputums sample for AFB (Acid fast bacilli) smear examination and on one of the specimen culture was applied. Bronchoscopy and bronchial wash was done in patients who were not expectorating. Bronchial wash was then applied for both smear and culture of mycobacterium tuberculosis.

All samples were decontaminated with N-acetyl-L-cysteine (NALC) sodium hydroxide according to standard protocol. The sediments were used for AFB microscopy and culture.

Smears for microscopy were screened using Auramine Rhodamine staining, positive slides were further confirmed by staining with Kinyoun modification of Ziehl-Neelson stain.

For TB cultures, LJ and MGIT (Becton Dickinson) were used. For LJ slant 0.1 ml of concentrated specimen was inoculated and incubated for 8 weeks. Suspected colonies were identified on the basis of conventional tests. Specimens in BACTEC and MGIT were inoculated as per manufacturer's recommendations.

Antimicrobial susceptibility for anti tuberculosis drugs except Pyrazinamide tested using modified agar proportion method according to Clinical Laboratory Standards Institute (CLSI). Pyrazinamide was tested using BACTEC 12B according to manufacturer's recommendations.

MTB H37Rv was used as control with each batch of susceptibility testing.

In the final analysis, only culture positive cases for M. tuberculosis were included.

Results

A total of 79 cases were recruited initially. Fifty-two were able to produce sputum while bronchoscopy was performed in the remaining. AFB direct smear was positive in 32/52 sputums and 12/27 bronchial wash samples. AFB direct smear was positive in 32 sputum samples while 12/27 bronchial wash samples were also positive. Later, 02 sputum and 04 bronchial washes specimens turned out culture positive, which were initially smear negative. All cultures were of Mycobacterium tuberculosis species. These fifty culture positive cases were then included in the final analysis.

There were 33 male and 17 female with median age of 33 years (range 15-55 years). The commonest presentations were cough (100%), fever (68%), sputum (64%) and tiredness (58%).

Table shows the resistance against first line drugs. Sensitivity against Rifamycin was available in 44 patients and all isolates were sensitive. MDR was seen in 02(04%).

Twenty-five (50%) isolates were sensitive to all five drugs. 18/50(36%) were resistant to one drug, 05/50 (10%) were resistant to two drugs and 02/50 (04%) were resistant to three drugs. The latter group was also resistant against Rifampicin and Isoniazid i.e. Multi-Drug Resistant tuberculosis (MDR-TB). Not a single isolate was resistant

Table. Primary resistance against first line drugs.

Anti-TB Drugs	Resistance
Streptomycin	13/50(26%)
INH	08/50 (16%)
Ethambutol	08/50 (16%)
Rifampicin	04/50 (08%)
Pyrazinamide	01/50 (02%)

against both streptomycin and Isoniazid.

Discussion

This study has shown significant resistance against first line drugs. The resistance against streptomycin is highest (26%), followed by INH (Isonicotinic acid hydrazide) and Ethambutol (16% each). This high resistance is alarming and could be due to the use of these drugs for a longer duration. Other reasons could be erratic prescriptions by health care providers, manipulation of medications by the patients, increase use of INH and Ethambutol in the continuation phase and indiscriminate use of streptomycin by General Practitioners and health care providers for conditions other than tuberculosis.

The locally reported data[2-4] about resistance against INH (13.3 to 16%) correlates with our study. Sadique and Suhail[2,3] have reported low resistance against Ethambutol (Zero%) and Streptomycin (3.7&11%), which is unreliable because of small sample size in their study. It is recommended that to determine low resistance rate, surveillance of large sample size is needed i.e. 300-600 specimens.[5]

In this study, the resistance against one or more first line drugs is 50% which is high in comparison to the reported 17% and 24% by Khan J[6] (1993) and Rano Mal et al[4] (2000) respectively. Both of these reported studies were done in Karachi so it seems likely to represent the same population. Sohail Akhtar[7] from Karachi reported primary and initial resistance to at least one drug by 7% and 21% respectively.

Shamshad R[8] from Lahore reported 52.16% resistance to one or more first line drugs that is comparable to our study. When comparing this study with Rano Mal et al, mono-resistance was 39% v/s 20%, resistance against two drugs was 10% v/s 04% and resistance against three drugs was zero v/s 04%. MDR (Multi-Drug Resistant) tuberculosis was 04% v/s 01%. These entire figures suggest an increasing trend in resistance.

The trend in resistance pattern against INH remains static since 1993[6] while resistance against Rifampicin has increased in the same period from 03% to 08%. Interestingly the resistance against Rifampicin is static since 2000.[2-4]

The data from our neighboring country India[9] is similar as far as resistance against streptomycin and INH is concerned i.e. 7.2-12.4% and 15.2-23.4% respectively. They reported low resistance against Ethambutol 01-4.6% and Rifampicin 0.5 - 2.8% in comparison to our study.

The data from remaining parts of the world[9] reveal highest primary resistance against streptomycin i.e. 21.7% to 44.3% from Lithuania and Uzbekistan respectively. The findings are similar to our study. The reported resistance against INH from China (Henan), Turkmenstan and Mongolia are similar to our results i.e. 17%, 15.2% and15.3% respectively while Kazakhstan have shown highest resistance (42.6%). The resistance against Ethambutol is lesser than China, Turkmenistan, Egypt and Mangolia ie from 1.7 to 4.3. Higher rates were reported from Estonia, Uzbekistan and Kazakhstan (13.2 to 24.8%). The resistance against Rifampicin varies between 1.2 and 15.6% from Mangolia and Kazakhstan. In this report9, sensitivity against Pyrazinamide is not done.

The MDR tuberculosis in this study is 4%. Sohail Akhtar[7] in his series (January 1999 to March 2003) reported zero MDR case while Rizwan et al[10] from Lahore reported 12% primary MDR. Recently Seema et al[11] from Karachi (January - September 2004) reported 10% primary MDR. In other parts of the world8 the reported MDR tuberculosis ranged 9.3%, 10.4%, 12.2%, 13.2% and 14.2% from Latvia, Liaoning, China, Estonia, Uzbekistan and Kazakhstan respectively. In India it is 0.5-2.8%.[9]

The possible reasons for the increase in resistance in our country are poor compliance, ignorance on the part of patients, over the counter sale of anti-tuberculosis drugs, poor quality anti-TB drugs, unpredictable supply of anti-TB drugs in public hospitals and non-standardized regimens. Masroor et al[12] reported that low socioeconomic status, improper dose schedule, under dosage and lack of health education apparently seemed to be responsible for most cases of drug resistance. Ziaullah et al[13] reported his drug-resistant cases to be among low socioeconomic status people. He added that ninety-five percent of cases had a history of treatment at least once, hence concluded that the resistance was of acquired type.

It has been reported[9] that Pakistan has achieved 100% DOTS (Directly Observed Treatment Short course) coverage in public sector in May 2005 heading towards a hope for controlling TB. But at the same time there is a need to involve Private Practitioners with the Provincial TB Control Program (Public Private Partnership) in an organized line[14] because it is estimated that from amongst the TB patients seeking treatment approximately 80% initially report to their private practitioners for their diagnosis and treatment.[15]

The weaknesses of this study are: small sample size, hospital-based study and lack of a reference laboratory.

Conclusion

There is high prevalence of primary resistance against streptomycin, INH and Ethambutol. The small sample size could not allow generalizing these results.

There is an urgent need to evaluate nationwide primary resistance pattern so that strategy in the treatment of tuberculosis be planned especially the use of Ethambutol and INH in the continuation phase of category-I treatment.

References

1. Country profile: Pakistan; Global tuberculosis control: Surveillance, Planning, Financing WHO report 2006, pp 110-2.
2. Sadique A, Presented at 23rd International conference on Tuberculosis & lung Diseases, IUATLD-Eastern Region, Lahore, Pakistan 25-28 Sep. 2005 (Not published).
3. Almani SA, Memon NM, Qureshi AF. Drug - Resistant Tuberculosis in Sindh. J Coll Physicians Surg Pak 2002; 12: 136-9.
4. Mal R, Nadeem R, Shahina Q. Primary drug resistance to anti-tuberculosis Drugs in Karachi, Pakistan. SAARC J TB Lung Dis & HIV 2004: 1: 20-23.
5. WHO/IUATLD. Global working group on anti-tuberculosis drug surveillance. Guidelines for surveillance of drug resistance in tuberculosis. Geneva: WHO, 1997. WHO / TB / 96.216.
6. Khan J, Islam N, Ajanee N, Jafri W. Drug resistance of mycobacterium tuberculosis in Karachi Pakistan. Trop Doct 1993; 23: 13-4.
7. Akhtar S, Haidri FR, Memon AM. Drug resistance to tuberculosis in a tertiary care setting in Karachi. J Pak Med Assoc 2007; 57: 282-4.
8. Rasul S, Shabbir I, Iqbal R, Haq M, Khan S, et al. Trends in Multi Drug Resistant Tuberculosis. Pak J Chest Med 2001; 7: 21-8.
9. Global tuberculosis control: surveillance, planning, financing. WHO report 2006. Geneva, World Health Organization.
10. Iqbal R, Shabbir I, Khan S, Mirza M, Awan SR, Hasan M. Pattern of drug resistance in Tuberculosis. Pakistan J Med Res 2005;44:136-9.
11. Irfan S, Hassan Q, Hasan R. Assessment of resistance in multi drug resistant tuberculosis patients. J Pak Med Assoc 2006; 56: 397-400.
12. Masroor M, Ahmed I, Qamar R, Imran K, Aurangzeb, Tanveer, et al. Prevalence and pattern of resistance to anti Tuberculosis drugs in our community. Pak J Chest Med 2007;13: 21-30.
13. Zialluah, Basit A, Javaid A. Pattern of drug resistance in pulmonary TB patient in NWFP. Pak J Chest Med 2006; 12: 11-6.
14. Guideline for the programmatic management of drug-resistant tuberculosis. WHO 2006 WHO/HTM/TB/2006.361.
15. Introduction; National Guidelines for TB control in Paksitan. 2nd ed. Islamabad 1997, pp 1-3.