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DRUG RESISTANCE PATTERN OF MYCOBACTERIUM TUBERCULOSIS IN KARACHI

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ABSTRACT:

BACKGROUND: *Tuberculosis (TB) is one of the common diseases in our country. Inappropriate antituberculosis therapy (ATT) has lead to emergence of resistance to mycobacteria.*
DESIGN: *A case series of 41 out door patients with sputum smear positive for pulmonary tuberculosis.*
METHODS: *41 patients attending out patient department of Imam Zain-ul-Abidin Hospital & Sarfarz Rafiqui Shaheed Hospital Karachi & diagnosed as pulmonary TB on clinical & investigational grounds were included in study. Sputum of all patients was positive for AFB staining. Sputum of all these patients was sent for mycobacterial culture & sensitivity.*
RESULTS: *41 patients, 23(56.1%) male & 18(43.9%) females were included in study. All patients had positive sputum smear for AFB. Culture for mycobacteria was positive in 37(90.24%) patients. Only 2(5.41%) patients were sensitive to all drugs. Highest resistance was observed to rifampicin & streptomycin 51.35% each. Resistance to isoniazid(INH) was 5.40% and to ethambutol was 8.10%. 2(5.41%) patients were found resistant to both INH & rifampicin i.e. Multi Drug Resistant Tuberculosis(MDR-TB).*
CONCLUSION: *Drug resistance to mycobacteria is increasing irrespective of number/ combinations of drugs used.*

KEY WORDS: Tuberculosis, MDR-TB, Drug resistant tuberculosis, Antituberculosis therapy.

INTRODUCTION:

Tuberculosis (TB) is medical, social and economic disaster of immense magnitude that is occurring the world over.[1] It should have been controlled after discovery of antituberculosis drugs, but still it remains one of the major killers, which caused death of 1.7 million people globally in 2009.[2] Pakistan ranks 6th amongst the high TB burden countries of the world. Pakistan contributes 44% of Tuberculosis burden in the Eastern Mediterranean region. According to WHO, the incidence of sputum positive TB cases in Pakistan is 80/ 100,000 per year and for all types it is 177/100,000.TB is responsible for 5.1 per cent of total national disease burden in Pakistan. [3]

Pharmacologic treatment of TB began after the discovery of streptomycin in 1944. It was almost same period when Para aminosalicylate (PAS) was brought into use. In 1952, after discovery of Isoniazid (INH), physicians started to give combination of these three drugs for 18 months. Later on, discovery of Pyrizinamide (PZA), ethambutol & rifampicin resulted in further reduction in treatment duration.[4]

Unfortunately, success in drug treatment of TB worked as catalyst for emergence of new wave of drug resistance. The terminology of Multi drug resistant TB (MDR-TB) was brought into practice, which is defined as "Resistance of mycobacterium TB to both rifampicin and INH with or without simultaneous resistance to other drugs".[5] Inadequate primary treatment regimen, non-compliance and addition of single drug to failing regimen predispose the patients to the development of MDR-TB.[6]Extensively drug resistant TB (XDR-TB) is new term describing the development of resistance to 2nd line drugs on top of MDR-TB.[7] Early detection and treatment of MDR-TB remains the most effective method to prevent its further spread.[8]

Our study was aimed to detect the current drug resistance pattern of mycobacterium tuberculosis strains to rifampicin, INH, ethambutol & streptomycin. This will help in

evaluating efficacy of our current treatment regimens which are based mainly on these four first line drugs.

MATERIALS AND METHODS:

We included patients attending outpatient department of Imam Zain-ul-abdin Hospital & Sarfaraz Rafiqui Shaheed Hospital Karachi, during the period from 2006 to 2009, from different parts of Karachi. Clinical suspicion of Pulmonary TB was based upon clinical features & investigations suggestive of TB such as low grade fever, malaise, weight loss, night sweats, productive cough, positive finding on examination of chest, anemia & raised ESR. Chest X ray, postero-anterior view of all patients was taken & sputum of all patients were sent for presence of acid fast bacilli(AFB) on Ziehl-Neelsen staining. Only inclusion criterion in our study was sputum positivity for acid fast bacilli, irrespective of their past history of tuberculosis or its treatment , so as to assess the overall drug resistance pattern of tuberculosis patients attending the outpatient department. Their sputum was sent for culture of Mycobacterium Tuberculosis & determination of resistance to ethambutol, INH, rifampicin & streptomycin. These drugs were tested by organ dilution method on Lowenstein-Jensen medium. Resistance ratio method was employed sensitivity interpretation.

RESULTS:

A total of 41 cases, between the ages of 14 to 82 years, were studied, 23 (56.1%) male & 18 (43.9%) female. Sputum for AFB was positive in all patients. However, growth of Mycobacterium Tuberculosis, was obtained in 37 patients (90.24%). Table 1 shows the drug sensitivity pattern of culture positive patients and Table 2 shows the resistance pattern of individual drugs. Culture & sensitivitiy results showed that 43.24% isolates were resistant to at least two antituberculous drugs. Two (5.41%) were found resistant to both INH & Rifampicin (i.e. MDR)

TABLE 1:
Drug Sensitivity Pattern for AFB Culture Positive Patients.

Sensitivity Pattern	Culture Positive Patients 37 (85%)
Sensitive to all drugs	2 (5.41%)
Resistant to 1 drug	15 (40.54%)
Resistant to 2 drugs	16 (43.24%)
Resistant to 3 drugs	2 (5.41%)
Resistant to 4 drugs	2 (5.41%)

TABLE 2:
Resistance of AFB to Individual Drugs.

Antituberculous Drug	Resistant Isolates
INH	2 (5.41%)
Rifampin	19 (51.35%)
Ethambutol	3 (8.10%)
Streptomycin	19 (51.35%)

DISCUSSION:

In our study 41 outdoor patients of pulmonary TB were selected. All of these had positive sputum smear for AFB as it was the inclusion criteria, however, only 37(90.24%) showed mycobacterial growth. Kuaban et. al. has reported that out of 111 sputum smear positive patients, mycobacteria were grown in 98(88.3%) patients on culture.[9]. Culture negativity of specimen, positive on AFB smear, may be due to the presence of artifacts on staining, identification of dead mycobacteria on smear, technical faults in culture and problems due to lack of expert personnel. This emphasizes the need for the development of standard laboratories with necessary infrastructure and expert personnel to exclude cases of negative culture with confidence.

Previous studies have shown that MDR tuberculosis is common in our country. Study conducted in 2004 by Butt T et. al, at Armed Forces Institute of Pathology, Rawalpindi showed 19% resistance to streptomycin, 37% to INH, 32% to rifampicin & 17% to ethambutol.

Among these 28% showed MDR.[10]

In contrast, in our study frequency of mycobacterial resistance to rifampicin & streptomycin was high (both 51.35%) while frequency of mycobacterial resistance to isoniazid was low (5.40%). Mathur ML et. al. in 2000 showed drug resistance to isoniazid was 16.67%, ethambutol 6.67% & rifampicin 6.67% in Jodhpur, India.[11]

A similar study was conducted in 2002 by Almani SA et. al. at Liaquat University of Medical & Health Sciences, Jamshoro. They analyzed primary & secondary drug resistance to Mycobacteria separately and found secondary drug resistance to be higher (53.33%) as compared to primary drug resistance (46.66%). Primary resistance was 13.33% to rifampicin & 11.11% to streptomycin & no strains were found resistant to rifampicin & ethambutol. Secondary resistance was 46.66% to isoniazid, 26.66% to streptomycin, 22.22% to ethambutol & 24.44% to rifampicin.[12] These results show that drug resistance is increasing alarmingly showing wide variation in resistance pattern in different parts of region.

The pattern of resistance observed in our study is different from other studies mentioned earlier specially with regard to resistance to streptomycin & rifampicin, & reduced incidence of MDR-TB (5.4%). However our results match with WHO report, of MDR-TB of 5% during last decade.[2] Emphasizing that now it is high time to consider every patient individually & send culture & sensitivity of mycobacteria in every case.

It is believed that maltreatment is principal cause of emergence of drug resistance.[13] Patient non-compliance is considered the most common reason for maltreatment. However, health care providers also play role in development of resistance. In Pakistan tuberculosis is mostly diagnosed on clinical suspicion and on therapeutic response to antituberculosis drugs, rather than on basis of culture isolation. This results in inappropriate use of antituberculosis drugs. Shamshad et. al. in their study " Family doctors & Tuberculosis control" interviewed two groups of doctors, 87 practicing in community and 25 appearing in Punjab Public Service Commission(P.P.S.C) for the post of medical officer. When asked to prescribe treatment for TB patients, only four from each group (4.6% in general practitioner and 16% of those appearing in P.P.S.C) could prescribe adequate regimen.[14,15]

Keeping above facts in mind, in view of the results of our study, we recommend that every effort should be in all patients of

tuberculosis for sending culture and sensitivity, so that by the time we reach continuation phase, we know the sensitivity pattern and change the treatment accordingly. There is also need for the development of state of art facilities for AFB culture & sensitivity so that it is easily available with minimum chances of technical failure.

CONCLUSION

Drug resistance to mycobacterium is increasing irrespective of number or combination of drugs. Specific resistance patterns like MDR are not significant in our study.

Rifampicin & streptomycin are more than 50% resistant in out door open tuberculosis patients and this observation along with the fact that rifampicin is main first line drug, in both intensive & continuation phases, will increase the treatment failure rate & frequency of resistance even in compliant patients with very well written prescriptions.

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