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A STUDY ON DRUG RESISTANCE PATTERN OF OSTEOARTICULAR TUBERCULOSIS

Orthopedics

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INTRODUCTION:

Osteoarticular tuberculosis involves 2-5% of all tubercular lesions in the body.[1] Out of which 50% affect spine.[1] The diagnosis of osteoarticular tuberculosis is clinico-radiological, particularly in the endemic regions. The typical lesion can be diagnosed clinico-radiologically with support of newer imaging modalities like computed tomography/magnetic resonance imaging (CT/MRI); however, tissue diagnosis is a must when there is a slightest doubt. For accurate diagnosis to be established the tubercular bacteria must be recovered from the lesion.[2]

The last few decades have seen a remarkable increase in incidence of drug resistance in Mycobacterium tuberculosis. From single drug resistance we have reached the era of multidrug resistance and extensive drug resistance. Multidrug resistant (MDR) tuberculosis is defined as tuberculosis caused by M. tuberculosis resistant in vitro to the effects of isoniazid and rifampicin, with or without resistance to other drugs. Extensively drug resistant (XDR) tuberculosis is defined as MDR tuberculosis which is additionally resistant to at least one of the fluroquinolones and to one of the three injectable second-line anti-tubercular drugs: amikacin, kanamycin, and capreomycin [2,3,4,5,6].

Resistance to any one anti-tuberculosis drug is termed as monoresistance whereas resistance to more than one antitubercular drug, other than both isoniazid and rifampicin is called polyresistance [2]. The main factors attributed to the development of drug resistance include inadequate and incomplete treatment, non-adherence to treatment, and genetic factors [2,3,8,9,10]. Short course chemotherapy with resistant/partially resistant drugs in resistant strains may create even more resistance to the drugs in use, and this has been called as the "amplifier effect" [2]. Ongoing transmission of established drug resistant strains in a population is also a significant source of new drug resistant cases [2]. The routine use of tuberculosis culture sensitivity in a suspected case of osteoarticular tuberculosis appears to be a probable solution to this ever increasing problem. Drug resistant form of osteoarticular tuberculosis is ill reported in the literature[7]. The diagnosis, management thus remains a challenge to the treating surgeon. The study include a series of cases that are drug resistant osteoarticular TB on the basis of clinico-radiological findings and Evaluation with further investigations (including cultures for mycobacteria) used to assess pattern of drug resistance,. This data from a local population can be quite helpful in setting up guidelines for formulating regimens for empiric management of cases with repeated negative cultures in an unresponsive patient or places where standard culture sensitivity facilities are not available.

MATERIALAND METHODOLOGY:

This is an observational cross sectional study to analyze the demographics of drug resistant osteoarticular tuberculosis in patients attended outpatient/in patient department at P. D. Hinduja National Hospital Mumbai between 2000-2014. 110 patients who were diagnosed to have drug resistant osteoarticular tuberculosis on the basis of their drug sensitivity testing patterns were studied. Hospital ethics committee clearance and waiver consent was taken before proceeding on this study. Patients with clinical and radiological diagnosis of osteoarticular tuberculosis and those drug sensitivity pattern shows resistance to at least 1 antitubercular drug were included in the study. Those who had negative culture on biopsy, doubtful diagnosis and drug sensitive osteoarticular tuberculosis were excluded from the study.

Data retrieval system of the institute was used to retrieve the demographic and clinical, drug susceptibility pattern of the patients diagnosed to have tuberculosis. Method of collection of sample, whether open surgical or radiologically guided, was noted. All samples were processed using the BACTEC MGIT (Mycobaterium Growth Indicator Tube) 960 system: a rapid, in vitro, non-radiometric system for rapid detection of mycobacterial growth as per the oxygen consumption[11]. Positive cultures could be grown between 10 and 21 days. Negative cultures were declared in case of inactivity for 42 days. The culture colonies isolated were of M. tuberculosis complex which comprises of M. tuberculosis, Mycobacterium bovis, Mycobacterium africanum, and Mycobacterium microti [12]. Demographic data including the age, sex, profession, and regional address of the patient were noted. Prior history or contact to a known case of tuberculosis/MDR-TB was recorded to drive insight into the endemic problem of this morbid disease. Medical history and previous drug history pertinent to antituberculosis chemotherapy was noted to determine the drug interactions.

Out of 650 positive cultures evaluated, 110 were found to have drug-resistant strains to at least one anti-tubercular drug. In 47% patients were male and 53 % patients were female. Average age 26.72 years (Range being 5 years to 64 years). Maximum frequency of patients seen in 11-20 age group (40%), Most of our patients (84%) were in the productive years of life. 54 patients (52%) were less than 20 years of age. In our study, Drug resistant tuberculosis of spine was seen in 31.62% cases, calcaneum osteomyelitis in 9.41% cases and SI joint, foot, tibia, ankle joint were involved in 8 % cases each. Elbow joint, hip joint, knee joint, ulna, femur were involved in 4.01% cases, and shoulder joint, illium, gluteal abscess were involved in 2% cases.

Multifocal tuberculosis (>1 bone involved) was seen In 23% patents , it was . Single bone involved In 77% patients, past history of pulmonary tuberculosis was seen in 28% cases, and past history of pulmonary + lymphnode TB, potts spine, tubercular meningitis was seen in 4% cases each, 60% cases were seen in our study with no previous history of tuberculosis. history of immunosuppression present in total 2 patients (8%), 1 case of hogkins lymphoma, 1 case was on chemotherapy and radiotherapy and rest of the patients did not have any other comorbidities. Most cases (76%) were subjected to formal open biopsy in order to obtain adequate representative tissue.

Out of the 110 drug-resistant cases, 78 patients had MDR strains (72%), 5 had XDR strains (4%) and 22 patient had monoresistance (20%), 5 patient were resistant to 2 drugs (non MDR). (table1, figure1)

Table 1

Resistence Pattern	No.	%
MDR	78	72.00
XDR	5	4.00
Single Drug Resistence	22	20.00
Two drug resistance(but not MDR)	5	4.00
Total	110	100.00

Figure 1

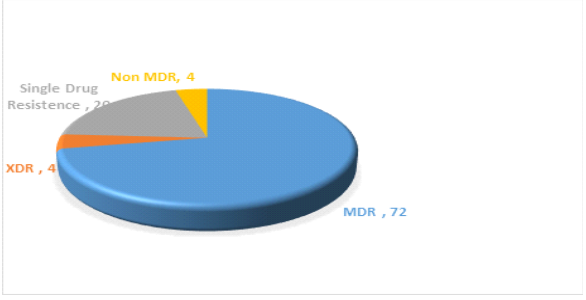


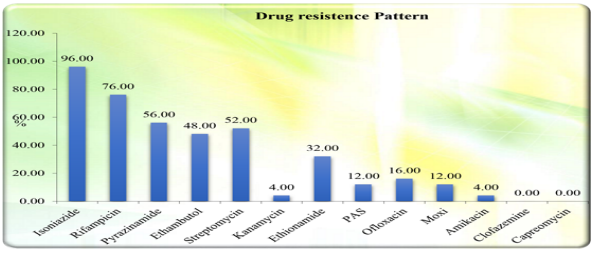
Table 2: Drug Resistance Pattern

Resistence Pattern (N=110)	%
Isoniazide	96.00
Rifampicin	76.00
Pyrazinamide	56.00
Ethambutol	48.00
Streptomycin	52.00
Kanamycin	4.00
Ethionamide	32.00
PAS	12.00
Ofloxacin	16.00
Moxi	12.00
Amikacin	4.00
Clofazemine	0.00
Capreomycin	0.00

***Multiple Response Table**

Among the first-line drugs, maximum resistance was found to isoniazid (96%) followed by rifampicin (76%), pyrazinamide (56%) and streptomycin (52%), Relatively least resistance was found against ethambutol (48%) among first-line drugs. Among the second-line drugs, maximum resistance was found against ethionamide (32%) and ofloxacin (16%) followed by PAS (12%), moxifloxacin (12%). Least resistance was against kanamycin (4%), amikacin (4%). No isolate was found to be resistant to clofazamine and capreomycin.

Figure 2:



DISCUSSION:

Multi drug resistance is a new dimension to the age old problem of osteoarticular tuberculosis. To the best of our knowledge, ours is the first and largest study that attempts to evaluate the drug-sensitivity patterns in drug-resistant osteoarticular tuberculosis. Traditionally, anti-tuberculous drugs are classified as first-line and second-line drugs, with isoniazid, rifampicin, pyrizinamide, ethambutol and streptomycin being the primary first-line drugs4,6. An alternative way of classifying anti-tubercular drugs can be based on efficacy, experience of use and drug class as mentioned in Table 313

Table 313

Group	Antitubercular drugs
First Line Anti-Tubercular Drugs	Isoniazide (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E), Streptomycin (S)
Second line: injectable agents	Kanamycin (Km), Amikacin (Amk), Capreomycin (Cm)
Fluoroquinolones	Levofloxacin (Lfx), Moxiflxacin (Mfx), Gatiflxacin (Gfx), Oflxacin (Ofx)
Oral Bacteriostatic Drugs	Ethionamide (Eto), Prothionamide (Pto), Cycloserine (Cs), Terizidone (Trd), p-aminosalicylic acid (PAS)
Group 5 Drugs agents with unclear role in treating drug resistant TB	Clofazimine (Cfz), Linezolid (Lzd), Amoxicillin/clavulanate (Amx/Clv), Thioacetazone (Th), Clarithromycin (Clr), Imipenem (Ipm)

The proportion of drug resistance found in our study is high and cannot be used to calculate epidemiological incidence as the study was conducted at a tertiary-level reference centre where most of the cases were those failing standard anti-tubercular therapy and hence the study population had a greater probability of harboring drug-resistant strains to begin with. Of the 110 patients of drug-resistant osteoarticular tuberculosis, highest resistance was found to isoniazid (105 patients: 96%) followed by rifampicin (83 patients: 76%) and pyrazinamide (62patients: 56%) followed by streptomycin (57 patients 52%). The results we got were different to that published by the WHO for pulmonary tuberculosis in 2008, which showed maximum resistance to isoniazid (13.3%), streptomycin (12.6%) and rifampicin (6.3%) [5]. However, WHO figures are for all patients with TB whereas we have only included the patients with resistant osteoarticular tuberculosis. Significant implication of this distribution is that among the first-line drugs, rifampicin which affects all populations of organism and isoniazid are the only drugs which are bactericidal and hence such a resistance pattern adversely affects the outcome after standard anti-tubercular treatment. 83 of the 110 patients had MDR strains (including 5 XDR), ethambutol showed the least resistance (48%) among the first-line drugs. Among the MDR group for the second-line drugs, resistance was high to ethionamide (32%) followed by ofloxacin (16%). Moxifloxacin and PAS (12%) showed intermediate resistance. Lowest resistance was to aminoglycosides: kanamycin and amikacin (4%), and no resistance was found to capreomycin and clofazamine. It should be noted that although both ofloxacin and moxifloxacin belong to the same class of drugs, i.e., fluoroquinolones, they have variable cross-resistance, and the presence of resistance to ofloxacin may not indicate resistance to moxifloxacin. However, amikacin and kanamycin show a high-degree of cross-resistance, hence if resistance to one is known, resistance to the other should be assumed [4,6]. There was a mean delay of 14.2 months between making the diagnosis and starting of appropriate treatment for drug resistant osteoarticular tuberculosis. Our pattern of drug resistance comparable with studies done by Litao Li et al[14] and Lan Xu et al[15] but diagnostic delay found higher in our study. The WHO–IUAT global drug resistance surveillance carried out in India between 1996 and 2002 reported the median prevalence of primary and acquired MDR-pulmonary TB to be 3.4% (1.8%–5.7%) and 25% (7.3%–52.3%), respectively. These studies were conducted in different states mostly in institutions and tertiary care centers and they do not reflect the overall status of drug resistance problem in India[16]. Similarly Almeda *et al* highlighted an alarmingly high percentage of multidrug-resistant *M. tuberculosis* isolates in an urban center (Mumbai-India) (51%) as compared with that at the rural center (2%).[17]There is paucity of data on prevalence of drug resistant osteoarticular system, only few study on drug resistant spinal tuberculosis. To the bes t of our knowledge there is no literature on this topic. While host genetic factors may contribute to the development of primary MDR-TB, incomplete and inadequate treatment is the most important factor leading to secondary drug resistance development, suggesting that it is often a man made tragedy.[20] The sources are many and the causes multifactorial. The treating physician, by his lack of knowledge regarding dosages, varied drug regimens followed by surgeons, side effects and standard regimens, and frequent change of brand names contributes to the problem.[18] In one of the studies where prescriptions of 449 physicians were analyzed, 75% of the physicians were found to have made some prescription error.[19]

Noncompliant patients due to monetary lack, lack of information, side effects of drugs, and social myths and misconceptions, often do not adhere to treatment. Comorbid conditions like diabetes, HIV infection, psychiatric conditions, the habits of smoking and alcoholism make the patient more vulnerable. To sum up, drug resistant osteoarticular tuberculosis usually results from inadequate drug therapy, inadequate knowledge of the prescribing physician/surgeon, difficulty in obtaining drugs by poor patients due to lack of financial resources or social insurances, frequent shortage of second line antituberculous drugs by poor management and/or financial constraints, use of drugs or fixed drug combination (FDC) of drugs with unproven bioavailability, lack of motivation at the beginning of treatment and inadequate self-administration of drugs without direct observation in the intensive phase of therapy[18]. The most common method of detecting drug resistant strains of tuberculosis is culture. This is not easily available in many countries and hence used only in patients with no response to the initial standard treatment regimen.[19] Therefore, detection of drug resistance is attempted only when there is a clinical suspicion of drug resistance. In 1 study, delay in starting appropriate MDR treatment after pulmonary TB diagnosis was 8 months if the drug susceptibility pattern of the source case was not considered.[20] Even in the present study a diagnostic delay of 14.2 months was noted The general treatment principles for MDR-TB according to the WHO criteria for pulmonary tuberculosis were followed which include: (*a*) Drug sensitivity testing, available from a reliable laboratory, should be used to guide therapy; (*b*) Regimens should consist of minimum 4 new drugs not used previously; (*c*) An injectable aminoglycoside should be used for a minimum period of 6 months; (*d*) Never add a single drug to a failing regimen-"Addition

Syndrome"; (*e*) Treatment should be for a minimum duration of 18 to 24 months[21,22,23]. Patients on second line drugs need to be monitored carefully for side effects. Gastrointestinal side effects are the most common. Drug induced neuropathies form a considerable group to the extent that pyridoxine should be an integral part of the regimen from the outset. Therefore the importance of regular and long-term follow-up to ensure compliance, to assess drug side effects and development of further resistance should be emphasized to the patient.[24,25] Sufficient data, again from pulmonary MDR-TB emphasize the fact that treatment of MDR-TB is difficult, complicated, much costlier, challenging, needs experience and skills of a specialized physician.

CONCLUSION:

In conclusion, our study highlights the growing threat posed by the development of resistance to antituberculous drugs in the management of osteoarticular tuberculosis. Complications arise due to delays in diagnosis and by inappropriate administration of drugs. Based on our findings, we recommend:-

(1) Having a high index of suspicion for the presence of drug resistance. Routine biopsy, culture and drug sensitivity testing of all patients.
(2) Use of drug susceptibility patterns wherever available to guide selection of appropriate second-line drugs.
(3) Consideration to be made to relative drug toxicities, efficacy and compatibility when selecting second-line drugs.
(4) Importance of regular and long-term follow-up to ensure compliance, to assess drug side effects and development of further resistance should be emphasized to the patient.
(5) Council and encourage patients not to stop treatment despite all its discomforts to prevent morbidity, mortality, and transmission of drug resistance.

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