A Prevelance of Drug- Resistance in Previously Treated Tuberculous Patients in Baghdad.

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ABSTRACT:

BACKGROUND:

Multi drug resistant tuberculosis (MDR-TB) is a majorpublic health problem because treatment is complicated;cure -rates are below those for drug-susceptible T.B., and patients may remain infectious for months or years despite receiving the best available therapy. The phenomenon of resistance was detected soon after the introduction of streptomycin for treatment of T.B.

OBJECTIVE:

To identify prevalence of MDR- TB patients in Baghdad.

PATIENT AND METHOD :

Across-sectional study, over a period of 1 YEAR (from January to December2012) had been carried out in Baghdad in order to identify the prevalence of drug-resistant tuberculosis in previously treated patients. 168 patients (112male and 56female) sputum smear positive patients were investigated at Chest and Respiratory institute by questionnaire about previous treatment then sent for drug susceptibility testing byegg-based solid medium of Lowenstein.

RESULTS:

An isolated drug resistance to streptomycin,isoniazid,Rifampicin and Ethambutul of 2.4% , 2.4% , 14.3% and 1.1% respectively. But MDR.TB.Of8.3 %(for more than one drug resistance).

CONCLUSION :

The high prevalence of M.D.R.T.B. and high prevalence of Rifampicin are the most alarming because of badmedical and social situation in Iraq now.

KEYWORD: multi-drug resistance tuberculosis.

INTRODUCTION:

Multi drug resistant tuberculosis (MDR-TB) is a major public health problem because treatment is complicated, cure -rates are below those for drug-susceptible T.B., and patients may remain infectious for months or years despite receiving the best available therapy. The phenomenon of resistance was detected soon after the introduction of streptomycin for treatment of T.B. (in 1944, streptomycin - an antibiotic newly isolated by waksman from the soil organism streptomycesgriseus).When the drug was given alone, a striking improvement in the patient's symptoms was observed at first, together with a rapid decrease in number of bacilli in the sputum, usually, the number of bacilli soon rose again and the patient's condition deteriorated. Bacilli isolated from the sputum of patients who had received streptomycin alone for few months (usually 12 weeks) were drug resistant, i.e.; the bacilli instead of being killed, continue to grow in vitro in the presence of high concentration of drug, the number of colonies in media containing 100 or 1000 M/ML of streptomycin approached the number of colonies in the control media without streptomycin[1].Furthermore, resistance to rifampicin result in substantial increase in the rate of failure and relapse when standard three of four drugs regimens are used[2] because it is the key sterilizing drug in short-course treatment of T.B[3]. In trails by British Medical Research Council, initial resistance of rifampicin has associated with failure rate of 45% during treatment, moreover, half of remaining patients relapsed giving overall rate if unfavorable treatment outcome of 72%[4].

Primary resistance is infection with a resistant strain, originating from a patient who has never taken drug in the past; while, acquired resistance occurs when a patient is posted cure-rates are below those for drug-susceptibleT.B., and patients may remain infectious for months or years despite receiving the best available therapy.

Resistance to a single drug through failure of the programmer to insure adherence to treatment or because of selective drug intake, irregular drug

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supply, poor drug quality or inappropriate prescriptions [5].

It is difficult to determine whether resistance is primary since the patients themselves may not know, or

may that they have had previous treatment for T.B.

The term acquired drug resistance implies that patients initially had drug susceptible organisms that developed resistance during the course of treatment. In practice, in most of the world where T.B. is common (including our country) reliable pretreatment drug susceptibility results are not available, furthermore, epidemiological evidence suggests that; some extents, most previously treated patients with drug resistance initially had primary drug resistance.

ALL AND RISE PHENOMENON:

In the bacterial population before start of treatment, the patient's sputum is positive by direct smear and the presence of large number of susceptible bacilli presented with a small proportion of mutant resistant strain (Figure 1).After the start of treatment, the total number of bacilli decreased rapidly (the drug-susceptible part of the population); whereas, the resistant part remains practically unaffected. In the second month, the total number of bacilli has decreased further more of the expense of the susceptible organisms. In the subsequent period, the total number of bacilli remains about the same; however, the structure of the population has changed fundamentally because the resistant mutant have gained the upper hand. During the next period, the resistant bacilli, new with a biological advantage rapidly outgrow the remaining drug susceptible bacilli. After about 5th month the mutant organisms have completely replaced the susceptible organisms; the strain become fully resistant, and the total number of bacilli is approaching the original number When the bacillary content dropped, further; the sputum

become negative by smear and positive only by culture is called «The fall».After certain time, the bacillary content increased again, the sputum again being positive by direct smear «The rise)). What is occurs in fact is the fall of susceptible bacilli and rise of resistant mutant of the strain[7].The (fall and rise) Phenomenon is prevented by use of appropriate multi drug regimen in the treatment of tuberculosis . Treatment regimens consisting of four drug during the initial phase and two during the continuation phase reduce the risk of selecting resistant bacilli. The main principle of multidrug regimen is that mutant resistant to a drug A (e.g.: rifampicin) are killed by drug B(e.g.: isoniazid) and mutant resistant to drug B are killed by drug A[8].It is postulated that resistance may arise because of treatment irregularity, without monotherapy, selection of resistant mutant could take place after different regimens have been administered, during which several cycles of killing and regrowth of resistant organisms occur, resistance could arise first to one of the drugs in the combination followed by the development of resistance to the other drugs, to produce a multidrug resistant strain[10].

PATIENT AND METHOD:

Across-sectional study had been carried out in Baghdad in order to identify the prevalence of drug-resistant tuberculosis. From January to December 2012, over a period of 1 year. We investigate 168 patients (112 male +56 females) at the Chest & Respiratory Diseases Institute by drug susceptibility testing.

The sputum smear positive TB patients were carefully interviewed by questionnaire to determine whether they have received prior treatment of TB or not with all information's about the age, sex, address, previous symptoms, previous treatment (completed or not and why stopped) and what are the recent symptoms.

Then the patients were sent to drug-susceptibility testing by egg-based medium of Lowenstein-Jensen (slopes of lowenstein -Jensen medium containing isoniazid 0.2 ML/L, dihydro streptomycin 4 Mg/L, rifampicin 40 ML/L and ethambutol 2 ML/L are prepared and stored at 4c° for maximum of 1 month).Temperature was examined daily because our electrical power was unstable.

We examine the seeded media for contamination after 1 week. The first reading of drug susceptibility test result was done 4 weeks (28 days) of incubation at 37 c°. All strains showing drug-resistance (growth of TB colonies on drug containing slope) were reported as drug resistant, other slopes need further reading of 6 weeks (42 days) before repairing susceptibility.

Resistance is expressed as percentage of colonies on drug containing media in comparison to the

growth on drug-free medium at Critical concentrations of the substances. The usual criterion for resistance is 1% of growth for all four drugs. The use of the term «borderline resistance is discouraged because it lead only to confusion overall cumulative sensitivity for drug resistant was 95%, specificity 95% and reproducibility 96%.

Table 1: Critical drug concentration and critical proportions for resistance (Lowenstein -Jensen medium).

Drug	Concentrati	Critical
Isoniazid	0.2 mg/ml	1%
Rifampicin	40 mg/ml	1%
Streptomyci	4 mg/ml	1%
Ethambutul	2 mg/ml	1%

RESULT:

A cross sectional study of 168 patients with smear positive pulmonary tuberculosis, we found that there are 48 patients (28.5%) out of 168 patient's drug resistance pulmonary tuberculosis classified as.

Single drug resistance34 patients (20.2 %), 26 male (15.4 %) and 8 female (4.8 %) .

Rifampicin carries a high percentage of resistance whichreflects misuse of this drug for other diseases, also male dominancy in single drug resistance as illustrated table 2.

Table 2: Illustrated Single drug resistance in previously treated TB patients.

Drug	No, of patients	Male	Female	Percentage %
Streptomycin	4	2	2	2.4%
Isoniazid	4	2	2	2.4%
Rifampicin	24	20	4	14.4%
Ethambutol	2	2	0	1%
Total	34	26	8	20.2%

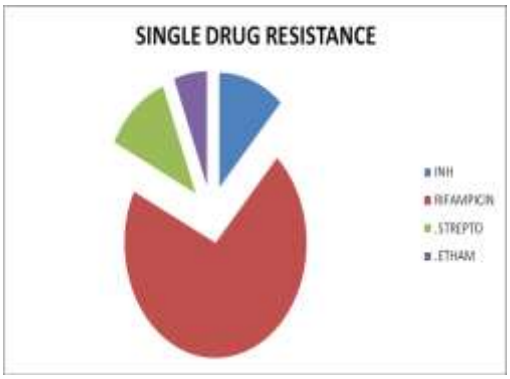


Figure 1: Illustrated Single drug resistance in previously treated TB patients.

Multidrug-resistant tuberculosis (MDR-TB) is defined as TB that is resistant to both isoniazid [INH] and rifampicin [RMP], two of the first-line drugs used in treating smear-positive pulmonary tuberculosis.

Extensively drug-resistant tuberculosis (XDR-TB) is defined by the WHO as MDR-TB with additional resistance to any fluoroquinolone (FQ) and to at least one of three injectable second-line anti-tuberculosis drugs used in treatment (capreomycin [CPM], kanamycin [KM] or amikacin [AMK]).

We found 14 patients (8.3%) , 8 female, 6 male ,presented with multiple drug resistance.

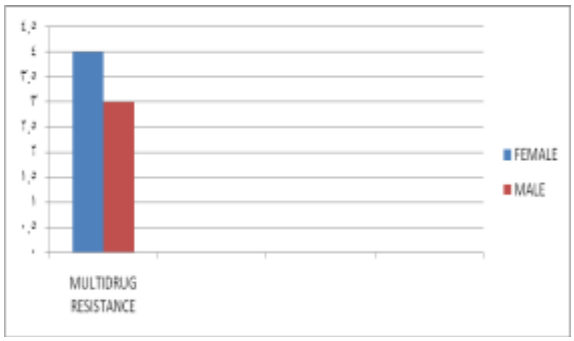


Figure 2: Sex distribution of multidrug resistance in TB patients.

DISCUSSION:

The prevalence of MDR-TB in 35 countries was surveyed by WHO in 1994-1997.The prevalence of MDR-TB was found to be related toquality of TB control program [21] Countries was classified as«better» or «poorer» TB control.

Better control defined as full coverage with direct observation therapy(DOTS), coverage of at least 1/3 of national territory, or TB notificationrate below 10 per 100.000 population any country that had unadapt DOTS, or that had a coverage of less than 13%of national territory was defined as having poorer TB control. Dataanalysis revealed that the prevalence of MDR-TB in countrieswith better TB control was 7.7%, as well as countries withpoorer TB control was 17%.

These observations suggest that proper TB control (achieved in effective DOTS programs) minimizes theemergence of MDR-TB where it does not yet exist.

African countries such as Benin, Botswana and Kenyawhich started using Rifampicin in their standardized short-coursetreatment regimens at the time of implementation of good Control practice and have achieved high cure rate, have beensuccessful in minim emergence and spread of MDR-TB, similarly, some Latin American countries such as Chile Cuba & Uruguay, with traditionally excellent control pronged curing most patients, today have very low levels of MDR-TB

On other hand, countries such as ivory coast, Dominic-republic, Estonia, Latvia, Russian federation (which used rifampicin widely before strengthen their program have a higher prevalence of MDR-TB thus, effective TB control prevents MDR-TB[22].

Iraq with a prevalence of MDR-TB of 8.3% will occupy the position between Ivanovo (Russia) & Dominican Republic with poorer T B control.

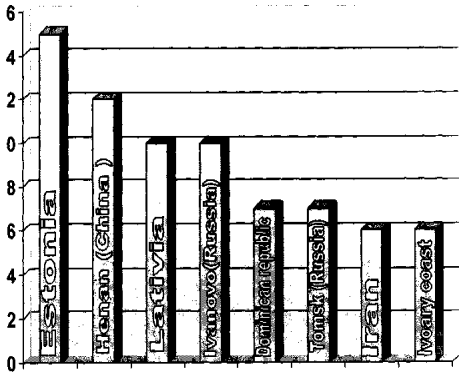
A study of MDR-TB in north Pakistan done by Bat Ahmad RN, Kazmi. SY, Rafi Nin, September 2004 indicated a prevalence of MDR-TB of 7 %[23].

Other study of MDR-TB in western Turkey by Komurcuoglu B, Komurcuoglu A, On May 2005 indicated a prevalence of MDR-TB 6.6% in Addition to a study of MDR-TB Bangladesh by /an* a* Rahim Z. on 2005 indicated a prevalence of MDR-TBOf5.5%.[25]

All these study revealed that the Iraq carries the highest prevalence in the region and this is the most alarming because of difficult medical & social situation in Iraq now.

In review of single drug resistance in Iraq shows that there is high prevalence of Rifampicin resistant TB (14.3%) which represents about 75% of single drug resistance.

Recent program shows that treatment success rates of rifampicin resistant cases are lower than that of drug resistant TB because it is a key sterilizing drug in the short treatment program.



Percentage of MDR-TB

CONCLUSION:

Drug resistant can be an important cause of treatment failure and death, particularly when to strains are resistant to the two main Bactericidal drugs isoniazid and rifampicin {multi-Drug resistant strains}.

Drug resistance developsas a result of inadequate or irregular regimen and Consequence of poorly organized programs.

Multidrug resistant strains can be transmitted in the community and replace susceptiblestrains, making first-line regimen inadequate for achieving high cure rates.

The high prevalence of multidrug resistant TB and highprevalence of rifampicin resistant TB in Iraq is to be most alarming because of bad medicalsituation {poor organized program).

Recommendations

1. Decentralization of treatment to the local health facilities and to the community, through health staff or trained and supervised community volunteers.
2. Reactivation of DOTS is very important and ensures of complete adherence of patients to the health system, and reduces the time from treatment interruption to recovery actions.
3. Use of adequate standard regimens. Government should choose national standardized treatment regimens based on efficacy data and operational experience and ensure that they are used by both public and private providers, and that the regimen are followed and achieve the expected outcomes
4. Use of fixed-dose combinations, which ensure that the patient take {all or none) of the drugs, facilities prescription and improves patient-acceptance.
5. Reduction of diagnostic delay through community information regarding symptoms, improved access to care, efficient procedures for collection and reporting of smear results.
6. considering rifampicin as an anti-tuberculosis drug only and instruct health staff not to use it another medical problems to decrease the prevalence of drug-resistance.
7. Encouragement to continue the researches drug resistant TB all over the country contains the problem and take quick actions of serious problem.

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