Prevalence of Drug Resistance among New Cases of Pulmonary Tuberculosis

Zaid Mohammed Ali Hamandi* ,Adnan M.Aljubouri**

ABSTRACT:

BACKGROUND:

Tuberculosis (TB) is a disease that has affected humankind throughout recorded history and before.Presently, the number of deaths caused by TB worldwide exceeds that caused by any other organism.

Drug-resistant tuberculosis is a man-made problem. Poor management can lead to the selection of M. tuberculosis with mutations conferring resistance to antituberculous drugs.

Drug resistance is divided into two types: primary (resistance in persons who have never received anti-tuberculosis drugs for more than 1 month. These patients are initially infected with drug-resistant strains) and secondary, acquired, (resistance to anti-tuberculosis drugs, which arises during treatment due to poor compliance or improper management.)

OBJECTIVE:

To identify the prevalence of drug resistance among new cases of pulmonary tuberculosis in Iraq.

METHODS:

A cross sectional studywhich includes, 106 patients fulfilled the criteria of inclusion throughout the duration of the study, and sputum samples were taken from all of them for direct microscopical examination and culture and drug sensitivity.

RESULTS:

Fifty patients (47.2%) had positive results for mycobacterial culture, none of them showed resistance to any anti- tuberculous drug that had been examined for, i.e. : all the 50 samples were sensitive to tested anti-tuberculous drugs

CONCLUSION:

standard first line treatment for pulmonary T.B. is recommended for all new cases of pulmonary tuberculosis in Iraq.

KEY WORDS: pulmonary tuberculosis, primary multidrug resistance.

INTRODUCTION:

Tuberculosis (TB) is a disease that has affected humankind throughout recorded history and before.Presently, the number of deaths caused by TB worldwide exceeds that caused by any other organism [(1)].

A among the mycobacteria there is a group of closely related microbes that is referred to as the "tuberculosis complex" which includes M. tuberculosis, M. bovis, M. Canetti, M. africanum and M. microti. They are generally distinguishable in term of natural reservoir, human pathogenicity and transmission patterns [(2).]

Soon after the drug was introduced, it was observed that although there was striking initial improvement in patients how received streptomycin, they subsequently worsened, and the organisms isolated from these patients were found to be resistant to streptomycin. The findings of clinical failure and emergence of drug resistance served to define the major bacteriologic principle on which successful chemotherapy for tuberculosis depends: Bacillary populations are not uniform in their susceptibility to antimycobacterial agents; hence it is always necessary to treat with more than one drug to which the organisms are susceptible [(3).]

The central drugs in modern regimens include the rifamycins (rifampin, rifabutin, and rifapentine), isoniazid, and pyrazinamide, regimens including these agents given for 6 months yield cure rate of 95% or more. Ethambutol or streptomycin is given to decrease the likelihood of failure or relapse in populations among whom there is a significant risk of initial resistance to one or more of the standard drugs [(2).]

*Baghdad Teaching Hospital, Medical City.
**College of Medicine, University of Baghdad.

Multi drug resistant (MDR) tuberculosis is defined as tuberculosis caused by an organism resistant to at least isoniazid and rifampin [4]. The treatment of multidrug-resistant tuberculosis is difficult due to side effects and treatment duration of up to 3 years, which is expensive and often unsuccessful. Therefore, strategies for the treatment and prevention of multidrug resistant tuberculosis are urgently required [5].

Drug resistance is divided into two types: primary and secondary (or acquired) resistance.

Primary resistance is defined as resistance in persons who have never received anti-tuberculosis drugs for more than 1 month. These patients are initially infected with drug-resistant strains [2,3,6].

Acquired resistance is defined as resistance arises during treatment due to poor compliance or improper management [4].

The WHO and International Union Against Tuberculosis and Lung Diseases (IUATLD) recommend to use terms drug resistance among new cases and drug resistance among previously treated cases [7,8].Drug- resistant tuberculosis is a man-made problem. Human error is the principal factor associated with the generation of drug – resistant strains of mycobacterium tuberculosis.The most common cause of drug resistant tuberculosis is undoubtedly the lack of a properly organized system to ensure effective treatment (i.e. national tuberculosis program), and particularly the lack of effective implemented directly observed treatment[6].

MATERIAL AND METHODS:

A cross sectional study conducted at the Chest and Respiratory disease institute, a referral center in Baghdad, Iraqduring the period extendingfromApril 2005 till May 2006.

Inclusion criteria, any patient with clinical and/or radiologicalsuspicion of pulmonary TB who, in response to direct questioning, denied prior treatment for one month or more and who had no documented history of treatment [9] [10].

According to the WHO recommendations [11] threesamples of sputum were taken fromeach of 106 patients who fulfilled the criteria of inclusion throughout the duration of the study, sputum samples sent for direct microscopicalexamination and culture and drug sensitivity at the same time, regardless the AFB examination results.

Data like; age of patient, history of contact to a known tuberculous patient, had been obtained by direct questioning of the patient himself, while other data like diabetes mellitus, hypertension, other cardiovascular diseases, medical reports were essential in addition to direct questioning.

RESULTS:

Forty nine patients (46.2%) had positive results for both direct AFB examination and culture examination, one had only direct AFB positive result and another one had only culture positive result, while fifty six patients (52.8%) had negative results for both, (table 1).

The mean age of patients was 34.5 year (+ 18.9 year), (table 2).

Male patients who had positive results among their group (68.6%) were more than female patients (27.3%) among corresponding group, this was statistically significant, (table 3)

Table 1: Distribution of direct AFB examination results according to positive and negative culture results.

	Direct AFB examination			Total
Culture results		+ve	-ve	
	+ve	49	1	50
	-ve	1	55	56
Total		50	56	106

Table 2: The minimum, the maximum, and the mean age of patients that had been examined in the study.

	Total no.	Minimum age	Maximum age	Mean age	SD*
Age (years)	106	8.00	87.00	34.54	18.90

*Standard Deviation

Table 3: Male and female number and percentages in both culture positive and negative groups.

			Gender		Total
			Male	Female	
Culture	-ve	No.	16	40	56
		%	31.4%	72.7%	52.8%
	+ve	No.	35	15	50
		%	68.6%	27.3%	47.2%
Total		No.	51	55	106
		%	100%	100%	100%

Chi square test; P value < 0.05

Table 4: Diabetes mellitus with sputum culture results, no statistical significance was found between the presence of diabetes mellitus and sputum culture results.

			DM		Total
			-ve	+ve	
Culture	-ve	No.	50	6	56
		%	50.0%	100%	52.8%
	+ve	No.	50	nil	50
		%	50.0%	nil	47.2%
Total		No.	100	6	106
		%	100%	100%	100%

Chi square test; P value ≥ 0.05

Table 5: Hypertension with sputum culture results, no significant association was found between the presences of hypertension sputum culture results.

			HT.CVD		Total
			-ve	+ve	
Culture	-ve	No.	55	1	56
		%	55.0%	16.7%	52.8%
	+ve	No.	45	5	50
		%	45.0%	83.3%	47.2%
Total		No.	100	6	106
		%	100%	100%	100%

Chi square test; P value ≥ 0.05

Table 6: Five different groups of patients with different CXR presentations in relation to sputum culture results, no statistical significance was found.

			Sputum Culture		Total
			-ve	+ve	
CXR	Normal	No.	10	5	15
		%	66.7%	33.3%	100%
	Cavity	No.	20	12	32
		%	62.5%	37.55	100%
	Apical density	No.	10	13	23
		%	43.5%	56.5%	100%
	Apical fibrosis	No.	5	5	10
		%	50.0%	50.0%	100%
	Apical pneumonia	No.	6	10	16
		%	37.5%	62.5%	100%
Total		No.	51	45	96
		%	53.1%	46.9%	100%

Chi square test; P value ≥ 0.05

DISCUSSON:

True rates of drug resistant tuberculosis (TB) throughout the world remain unknown, particularly in regions where the TB burden is greatest. This has been due principally to methodological problems including the absence of longitudinal studies to detect trends, failure to differentiate primary and acquired drug resistance in studies, the selection bias of many surveys, and the absence of high quality laboratory culture facilities [12].

Among fifty patients who had positive sputum culture for mycobacterium tuberculosis, none of them had resistant bacilli, this could be attributed to many reasons, and some of them are:

First, the median age of our patients was 34.5 years (± 18.9 years), and primary drug resistance known to be more in children as they get infected from adult source with drug-resistant TB [4].

Second, only 12 patients who had cavitary lesionson CXR,had positive culture results, it could be that more such patients will give more number of resistant cases [2].

As shown at the WHO Third Global Report (WHO), similar findings were reported over the world, the median number of cases tested per setting was 459. The number of cases tested ranged from 3 (Andorra) to 9751 (USA) [13].

Seventy-four countries/geographical settings provided data on the prevalence of drug resistance among new cases of TB. The overall drug resistance ranged from 0% (Andorra, Iceland, and Malta) to 57.1% (Kazakhstan), with a median of 10.2% [13].

One case, a negative culture was associated with positive AFB result, for a patient who had received treatment for fourteen days. A negative culture result with a specimen containing tubercle bacilli may be due to various causes. In patients receiving treatment, the organisms may have lost their ability to grow on culture media and be practically dead. Patients being treated with a rifampicin – containing regimen often become culture negative by about the third week of treatment, although they may still be sputum smear – positive: bacilli are dead or non-viable. In patients who have not had treatment, sputum specimens may have been exposed to sunlight or heat, stored too long, dried out, or contaminated.

Excessive decontamination procedures before inoculation, over heating during centrifugation, inadequate culture media, and deficient incubation may also results in a negative culture. In a few instances, positive smears may be caused by non-tuberculosismycobacteria [6].

More female patients (55) than male (51) had been examined for sputum culture, despite that, more male patients (35) had positive results than female (15).This difference was statistically significant, and it was independent factor.This finding, though being important, but cannot be explained now, it may follow certain geographical factor or it had been affected by sample size.

An earlier study showed male to female ratio of 5:1, though there was no explanation of it [14].

Six of one hundred six patients with documented medical reports of D.M., none of them had positive culture results; sample size could affect this result.While patients with hypertension and other cardiovascular diseases, 6 patients had documented medical reports, fife of them hadpositive culture results, it was statistically not significant could be because small sample size. Others found that Diabetes continues to be a risk factor for tuberculosis and wasassociated with MDR-TB [14,15].

A chest X– ray findings were not associated with statistically significant diagnostic yield, i.e.; no single type of CXR finding was associated with more diagnosis of pulmonary TB, and 23 patients had been labeled as having apical densities, it was not possible at time to categorized them as having pneumonias, fibrosis, malignancies, or other, follow up was necessary.

One finding that require attention was that 20 (62.5%) patients who had cavitary lesions at CXR, had negative sputum culture results, and12 (37.5%) patients of the same group had positive results, a previous CXRs were essential, follow up of patients with cavitary lesions for other diagnosis (e.g.; pneumonia, malignancy, vasculitis and others), previous medical reports of pulmonary TB, and laboratory factors. All these factors affecting the finding that the presence of cavitary lesion associated with large numbers of bacilli which are more rapidly proliferating and even more risk for resistance [2,15].

CONCLUSION:

The prevalence of drug resistance among new cases of tuberculosis, or primary resistance, in Iraqis patients is zero, so standard first line treatment for pulmonary tuberculosis is recommended for all new cases of tuberculosis.

There is no indication to recommend sputum culture for mycobacterium tuberculosis for a new case of TB as it added no much result over direct sputum examination using Ziehl-Neelsen stain.

There is no indication to recommend sputum culture and drug susceptibility test for new cases of pulmonary tuberculosis, as the primary resistance, or resistance among new cases, was nil.

A larger study is recommended, as this is the first study and a study with larger sample size, more duration, and more facilities will make these results more mature, in addition to that a another study after a given time may signify any change in drug sensitivity from this study.

REFRENCES :

1. Jay A. Fishman; Fishmans manual of pulmonary diseases and disorders, third edition, 2002;62: 763.
2. Michael D. Iseman, Current diagnosis and treatment in pulmonary medicine, Michael E. Hanley, Caroln H. Welsh, 2003;39 :399.
3. Philip C. Hopewell,Barry R. Bloom, Tuberculosis and Other Mycobacterial Diseases, Textbook of Respiratory Medicine, third edition, 1996;34:1065.
4. Philip A. LoBue _ Michael F. Iademarco _ Kenneth G. Castro, Fishman s Pulmonary Diseases and Disorders, 2008;132: 2451.
5. Loddenkemper, Sagebiel, Brendel: Strategies against Multidrug-Resistant Tuberculosis.EurRespir J 2002;20: Suppl. 36, 66s–77s DOI: 10.1183/09031936.02.00401302.
6. Frieden. ; Toman's tuberculosis case detection, treatment, and monitoring: questions and answers / edited by T. Frieden, 2000;Second Ed:45.
7. Kordy, al-thawadi: Drug Resistance Patterns of Mycobacterium Tuberculosis in Riyadh, Saudi Arabiaint j tuberc lung dis, 2004;8:1007–11.
8. Meaza demissie1, eshetu lemma, mekdesgebeyehu and berntlindtjorn: Sensitivity to Anti-Tuberculosis Drugs in HIV-Positive And -Negative Patients In Addis Ababa Scand J Infect Dis, 2001;33:914–19.
9. Christopher Dye, Marcos A. Espinal, Catherine J. Watt, CyrilleMbiaga, and Brian G. Williams: Worldwide Incidence of Multidrug-Resistant Tuberculosis, Communicable Diseases, World Health Organization, Geneva, Switzerland, 2002;3:114.
10. Marcosa. Espinal, .adalbertlaszlo, lonesimonsen, fadilaboulahbal, sangjaekimanareniero, svenhoffner, hansl. Rieder, nancybinkin, Christopher dye, phil., rosamundwilliams, and marioc. Raviglione: Global Trends In Resistance To Anti Tuberculosis Drugs For The World Health Organization–International Union Against Tuberculosis And Lung Disease Working Group On Anti-Tuberculosis Drug Resistance Surveillance N Engl J Med, 2001;344:26.
11. Isabel Narvaez de Kantor sang jaekimthomasfriedenadalbertlaszlofabioluel mopierre-yvesnorvalhansriederpedrovalnzuelakarin. Laboratory Services In Tuberculosis Control Microscopy Part llwriting committee: On a draft document prepared by: KARIN WEYERfor the Global Tuberculosis Program.World Health OrganizationGeneva, Switzerland 1998;sec1:11.
12. Ruddy, Balabanova, Graham, Fedorin, Malomanova, Elisarova, Kuznetznov, Gusarova, Zakharova, Melentyev, Krukova, Golishevskaya, Erokhin, Dorozhkova and Drobniewski: Rates of drug resistance and risk factor analysis in civilian and prison patients with tuberculosis in Samara Region, Russia Thorax 2005;60;130-135 doi:10.1136/thx.2004.026922
13. The WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance SurveillanceAnti-Tuberculosis Drug Resistance In The WorldThird Global Report1999-2002; section 3: 58.
14. Mona Bashar; Phil Alcabes,; William N. Rom and Rany Condos; Increased Incidence Of Multidrug- Resistant Tuberculosis In Diabetic Patients On The Bellevue Chest Service, 1987 TO 1997, Chest 2001;120;1514-19.
15. Joseph Loscalzo, HARRISON'S Pulmonary and Critical Care Medicine, 2010;12:118.