REVIEW ARTICLE

PRIMARY DRUG RESISTANCE TUBERCULOSIS

Mustafa Kamal, Arshad Javaid

ABSTARCT: The level of early drug resistance is an epidemiological marker to evaluate the success of the TB control program in Pakistan. Despite the fact, that Primary drug resistance in TB has repeatedly been reported from numerous areas of the world including Pakistan. An evaluation of the small number of reliable reports indicates that there is an obvious fact of an increase in the prevalence of early resistance over the years. As soon as drug resistance is confirmed in a patient who has not at all received anti- TB treatment earlier, it is named as primary resistance. Acquired resistance is that which takes place as an outcome of definite prior treatment. On the other hand, the World Health Organization (WHO) and the International Union against Tuberculosis and Lung Diseases (IUATLD), in the light of negotiations in numerous intercontinental debates, have substituted the word primary resistance by the term “drug resistance among fresh cases” and acquired resistance by the name “drug resistance among earlier managed case. Nevertheless, a lot high prevalence of acquired resistance has been reported from numerous areas of the world including Pakistan. Newer drugs for tuberculosis are improbable to come up in the near upcoming and therefore the input to achievement leftovers is satisfactory case finding, without delay and accurate diagnosis and efficient management of infective patients together with cautious introduction of second-line drugs to which the patient is vulnerable.

KEY WORDS: Primary drug resistance Tuberculosis; Pakistan; India; Africa; Western countries; Current status;

INTRODUCTION:

Drug resistance has been described as either primary or acquired. Primary drug resistance refers to resistance of strains segregated from patients who have not formerly received TB treatment[1]. Acquired drug resistance expressed TB isolated from patients who presently are getting or until that time have received anti-TB drug treatment for at least 1 month. Primary drug resistance is understood to be caused by the spread of drug-resistant strains. Molecular studies have revealed that the percentage of drug-resistant strains that are transmitted may be taken too lightly. In a study from South Africa using restriction-fragment length polymorphism scrutiny, countless of the patients with a history of earlier TB management had confirmation of transmission of a drug-resistant strain [2].For that reason, in epidemic regions, the terms primary and acquired resistance have been substituted by drug resistance among latest cases and drug resistance among formerly managed cases, respectively [2]. Drug resistance is additionally categorized by the drugs for which resistance is there (Table I) [3].

The amount of innovative cases that is Primary Drug resistance to at least one anti-tuberculosis drug (any resistance) ranged from 0 to 56%. Forty-five countries have stated at least one case of XDR-TB[4]. Huge breach of information is present in a few of the majority affected regions of the globe, such as of Africa, countries in the previous Soviet Union, and regions of Asia about Primary multidrug resistance TB. Roughly half of the accessible close watch statistics is from regions in which drug susceptibility testing (DST) is not consistently carried out.

Department of Pulmonology, Post Graduate Medical Institute, Lady Reading Hospital of Peshawar, Pakistan.

Moreover, DST for second-line drugs is not regularly executed in most countrywide reference laboratories.

DISCUSSION:

Drug resistance in tuberculosis is basically a man-made calamity caused by incorrect recommending practices on the part of physicians and noncompliance on the part of patients. These responses have recommended that available TB control measures were insufficient to control the transmission of drug-resistant TB in HIV co-infected and non HIV co-infected TB population. Delay in the identification of disease and improper treatment facilitated disease spread and Primary or acquired drug-resistance arise. These statistics call for better infection control measures, achievement of quick diagnostics, better active screening approaches, and pharmacokinetic studies to find out optimal dose and management course of therapy[5].

Spread of HIV viruses harboring resistance mutations is by now a key distress in industrial countries; with possible to impact on curative approaches and this alteration of tactic has had direct impact on the prevalence of drug resistant virus in the inhabitants and the spread of Primary Drug resistance Tuberculosis[6]. The incidence of tuberculosis has amplified countrywide and more than two fold in the precedent decade in the City of New York, where there have been recent nosocomial epidemics of Primary multidrug-resistant tuberculosis [6]. Scrutiny and clinical recognition of primary resistance is reasonable in the initial year of infection[7]. Schaaf et al [8] has evaluated the drug resistance incidence among children as compared to adults in Western Cape Province of South Africa. The incidence of drug resistance in childhood tuberculosis was low, and most likely imitates the height of primary drug resistance amongst organisms presently circulating in the group of people[8].

The prevalence of low level Primary drug resistant tuberculosis (TB) in Ethiopia in general and Jimma region in particular, is not acknowledged properly. A study was carried out at Jimma University specialized sanatorium in southwest Ethiopia among fresh cases of smear positive TB patients to establish the prototype of resistance to first-line drugs.136 patients were included in the study. Resistance to at least one drug was recognized in 18.4%. The maximum prevalence of resistance to any drug was recognized next to INH (13.2%) pursued by STM (8.1%). There was statistically no significant dissimilarity in the amount of any resistance by sex, age, HIV status and history of being jailed. Multidrug-resistance TB (MDR-TB) was documented in two patients (1.5%). INH resistance was widespread around Jimma and the resistance to STM was linked with positive HIV infection[9].

In Bangkok sanatorium a study was carried out to conclude human immunodeficiency virus (HIV) seroprevalence among patients with pulmonary tuberculosis (TB), and evaluate primary drug resistance TB among HIV-positive and HIV-negative TB patients. HIV prevalence was high among TB patients and is coupled with drug resistance, including a 12 times advanced risk of Primary MDR-TB. These conclusions highlight the critical need to declare adherence to full, effective TB therapy schedules for every one patients, who are potentially not easy to manage such as injection drug users and Suitable chemoprophylaxis may put off disease in these children[10].

A study conducted by Javaid et al [11] was to evaluate the prevalence of Primary drug resistance to antituberculous drugs in the Province of Khyber Pakthunkhwa (KPK), Pakistan. This cross-sectional prevalence study was undertaken to evaluate the prevalence of drug resistance among new TB patients, using a non-probability convenience sampling method. Sputum isolates were got from 122 recently identified patients of pulmonary tuberculosis from centers in Peshawar and Abbotabad in the Province of Khyber Pakhtunkhwa. In 118 patients,

Resistance to Streptomycin (10µg/ml) was observed in 7 (5.9%), Isoniazid (1µg/ml) in 10 (8.4%), Rifampicin (5µg/ml) in 3 (2.5%), Ethambutol (10µg/ml) in 2 (1.6%) and Pyrazinamide in 6 (5, 0%) sputum specimens. Primary Multidrug resistance was 2.5%, which is a cause of fear and be supposed to be dealt with through efficient TB control programmes with DOTS approach.

Sajdudal et al[12] has isolated a total of 105 Rifampicin resistant and/or Isoniazid resistant strains of Mycobacterium tuberculosis from different parts of Poland in 2000 were screened for mutations related with Primary resistance to these drugs by two molecular techniques, which are sequence analysis and real-time PCR equipment and have concluded that the real-time PCR technique is quick and consistent for the recognition of RMP and INH resistance-linked mutations in M. tuberculosis clinical specimens[12]. The conclusion of this study is quite alike to study executed by Abebe et al [13] , which had recognized that Primary multidrug resistance TB is present in the in the community with Capilia TB-Neo test[13].

To contrast the drug-susceptibility models of Mycobacterium tuberculosis isolated from patients (children) and from their consequent adult contacts was the foundation of the study by Steiner et al [14]. In 111 (92.5%) requests the creature isolated from the child and that from the grown-up contact had identical drug-susceptibility patterns. Fourteen (93%) of 15 of the adult/child pairs were together resistant to Isoniazid. The drug-susceptibility prototypes of isolates obtained from the source of a child's illness is useful as a guide in planning initial drug treatment. The results of this study are comparable to the study by Cohn et al[20]. They have time-honored a worldwide scheme of drug resistance study that is based on typical epidemiological techniques and excellence control during a widespread network of reference laboratories.

They require finding out if the susceptibility prototype of the isolate from the adult contact could be used as a guide in the early selection of the antituberculous therapy in the child, and adults were recognized who had positive cultures and who were the causative factors of the children's infections. A study carried out by Stephen et al [16] reveals that the administration of therapy for M. tuberculosis infection under direct watching leads to significant reductions in the frequency of primary drug resistance, acquired drug resistance, and relapse. A case reported by Sarkar et al [17] from West Bengal India is described here. A 37-year old man He was presented with back pain, low-grade fever and weight-loss. X-ray of chest (postero-anterior view) showed numerous opacities with corrosion of right 2nd and left 6th ribs. CT-scan of thorax and CT-guided Fine Needle Aspiration Cytology (FNAC) confirmed the finding of tuberculosis of ribs. Still after 5-months of treatment with four first line drugs, the patient developed a cold abscess at the back. Mycobacterium culture and drug sensitivity of objects aspirated by radiometric technique from the cold abscess demonstrated development of Mycobacterium tuberculosis, and those bacilli were resistant to both Isoniazid and Rifampicin. The patient did not have anti-tubercular tablets in the past and he was managed fruitfully with 2nd line drugs at the expenditure of reasonable degree of hearing loss. This case is clearly showing the presence of Primary multi-drug resistance extra pulmonary TB as well [17].

Descriptive study was carried out in two outpatient medical appointment clinics from January 1999 to March 2003 to evaluate the resistance molds of tuberculosis cases by Akhtar et al [18]. Statistics from 71 confirmed culture positive patients was obtainable. Resistance to at least one antituberculous drug was originated in 44 (60.5%) cases. Primary, Initial and Secondary Resistance to at least one drug was 7.0%, 21.1% and 32.3% respectively[31]. Out of 7.0% primary resistance patients, there was 5.6% of single medicine resistance, 1.4% several Drugs and zero percent of Multi drug Resistance (MDR). Solitary drug resistance (for primary,

initial and acquired) confirmed 14% resistance for Isoniazid, 4.2% for Rifampicin, 2.8% each for Ethambutol and Streptomycin and 1.4% to Pyrazinamide. They have accomplished that in their cohort of patients, Primary resistance to at least one drug was 7.0% and no MDR. Amongst individual drugs, resistance to Isoniazid was maximum (14%) and lowly for Pyrazinamide (1.4%). The results of this study is very similar to the studies done by Javaid et al [17, 39], but this study has not revealed any single case of Primary multi-drug resistance Tuberculosis. This might be of small sample size, but Akhter et al [31] and Javaid et al [17, 39], both were of the agreement that Primary TB is supposed to be dealt with through efficient TB control programmes with DOTS approach. Educating doctors about accurate drug regimens and testing codes of behavior should be done concurrently.

The primary resistance pace to four first-line antituberculosis drugs and Primary MDR-TB rate are disturbingly high, representing a disturbing condition in Najran. Additional studies are required for nonstop scrutiny of M. tuberculosis resistance prototypes. The study is carried out in Najran; Southwestern Saudi Arabia[19] was aimed to determine the rates and patterns of primary anti-TB drugs resistance. The study included 80 smear-positive new pulmonary TB patients. Sputum samples were cultured on Lowenstein–Jensen and Middle-Brook 7H10 media. Mycobacterium tuberculosis susceptibility testing was done by the conservative agar proportion technique for Isoniazid (INH), Rifampicin (RIF), Streptomycin (SPM) and Ethambutol (EMB). Out of the 68 M. tuberculosis isolates, 42 (61.8%) were sensitive to all 4 drugs and 26 (38.2%) were resistant to one or more drugs. The mainly widespread resistance was established to INH (33.8%), followed by RIF (23.5%), SPM (13.2%) and EMB (2.9%). Multi-drug resistant (MDR) sputum samples were originated in 14 (20.6%) cases. Primary antituberculous drugs resistance rate of 38.2% representing are an extremely upsetting circumstances in Najran. The rate of multidrug-resistant tuberculosis is upsettingly elevated and be supposed to be taken gravely in making a decision treatment codes of behavior in Najran[19].

Correct diagnosis of TB is wanted to get better treatment, lessen spread, and control development of drug resistance. Microscopic Observation Drug Susceptibility assay (MODS) classify the isolates as resistant. The (MODS) is a culture method shown to be more sensitive, faster and cheaper test than current culture-based tests for Tuberculosis. The MODS involves direct observation of Mycobacterium tuberculosis simultaneously yields drug-resistance [20]. Similarly, the Gene Xpert MTB/RIF identifies DNA sequences specific for Mycobacterium tuberculosis and Rifampicin resistance by Polymerase chain reaction [21, 22]. It is based on the Cepheid Gene Xpert system, a platform for quick and simple-to-use nucleic acid amplification tests (NAAT). It identifies all the clinically significant Rifampicin resistance inducing mutations in the RNA polymerase beta (rpoB) gene in the Mycobacterium tuberculosis genome. Results are acquired from unprocessed sputum specimens in 90 minutes, with minimal biohazard [23].

The reports of the first few patients being discovered with “totally drug-resistant “tuberculosis (TDR-TB) i.e., resistant to every first and second-line TB drugs in India in January did little to encourage the administration into acting positively. TDR-TB was primary reported from Italy in 2007 and Iran in 2009[24]. On the contrary, as in the case of the NDM-1 superbug case, its early reaction was on expected situate of throwing out and exposing the garbage. NDM-1, which stands for New Delhi metallo-beta-lactamase-1 is a gene (DNA code) carried by a few bacteria. If a bacteria strain carries the NDM-1 gene it is resistant to almost every antibiotics, including carbapenem antibiotics; also known as antibiotics of final resort. A bacterium with the NDM-1 DNA code has the potential to be resistant to every our existing antibiotics, as well as innovative antibiotics which may come into the market in the near future[25]. There is a

strong possibility of NDM-1 type of gene which might have lead to the occurrences of Primary TDR-TB.

According to Restriction Fragment Length Polymorphism (RFLP), there is much vagueness with the clinical word acquired drug resistance and should categorically be replaced with the term “drug resistance in formerly managed cases”[26]. According to the Centers for Disease Control (CDC), there were 14 cases of Primary MDR-TB in United States (US)-borne persons in the US in 2010[27]. For the reason that of the slow growth of M. tuberculosis, drug sensitivity by culture takes 4 to 8 weeks. Molecular detection of drug resistance (MDDR) can reveal sensitivities in one to two days. With early detection of MDR-TB; we can potentially lessen time of contagiousness, occurrence of Primary MDR-TB cases, morbidity/death, and health care expenditure[28].

For assessing the primary drug resistance of fresh culture positive cases of pulmonary tuberculosis in Karachi, Pakistan was carried out by Rao et al [29]. They had collected 79 cases and 55 cases were turn out to be culture positive for Mycobacterium TB. In this study Pyrazinamide was found to be the most sensitive drug i.e. 49 segregates (98%) were found to be sensitive to Mycobacterium Tuberculosis Specie. The resistance outline were that, 13(26%) of resistance were found to Streptomycin, Isoniazid 08 (16%), Ethambutol 08 (16%), Rifampicin 04 (08%) and Pyrazinamide one (02%). Multi-Drug Resistant tuberculosis strains were experiential in only 02 (04%) patients. The elevated prevalence of primary resistance against streptomycin, INH and Ethambutol in this small study had raised a critical need of an appropriate countrywide survey to appraise the accurate representation of primary resistance [38]. In respond to the study by Rao et al, a grand countrywide cross-sectional of 742 patients were carried out by Javaid et al [39]. To evaluate the prevalence of primary drug resistance in the country of Pakistan, sputum samples from 742 untreated recently detected patients of pulmonary TB from the entire country were collected and integrated in the study. Out Of 672 culture-positive patients, 76 (11.3%) had shown resistance to one or more than one drugs. in 36 (5.4%) of patients, resistance to streptomycin (10 µg/ml) was noted, in 51 (7.6%) of patients, Isoniazid (INH) (1 µg/ml) was found out, and in 15 (2.2%) of patients Rifampicin (RMP) (5 µg/ml) , resistance to Ethambutol (10 µg/ml) was established in 12 (1.8%) and in only 22 (3.3%) samples, resistance to Pyrazinamide was also noted. Total number of isolates tested for resistant to a single drug were found out to be 46 (6.8%), 10 (1.5%) had revealed resistance to two drugs, 12 (1.8%) had shown drug resistance to three drugs, and merely 6 (0.9%) isolates collected from patients included in the study had made known resistance to four drugs, whereas 2 (0.3%) isolates were resistant to every five first-line agents. Primary MDR-TB was found in 12 patients, which make 1.8% of all cases (INH 1 µg/ml, RMP 5 µg/ml). The results of the study done by Javaid et al [30] had demonstrated a prevalence of primary MDR-TB in Pakistan of <2%, which was comparable to the study executed by Rao et al [28]. Javaid et al had concluded from the results of the study that it requires to be dealt through a successful DOTS approach, which was previously thought by Stephen et al [31] as well.

In the year 2000, there was a strong remark that the Beijing genotype of Mycobacterium tuberculosis is budding in Vietnam. Study was carried out by Anh et al [32] and they have found out that 54% patients were infected with Beijing genotype strains. This genotype was linked with patient of younger age groups (and that's why with active spread) and with Isoniazid and Streptomycin resistance, except BCG immunization, which needs further studies to evaluate this Beijing genotype strains as the cause of Primary Drug resistance TB[32]. In Tarrant County of Texas, USA, a program was commenced about the worldwide directly observed treatment for tuberculosis by Stephen et al [31]. They have concluded that with DOT approach, that the

incidence of primary drug resistance had decreased from 13.0 percent to 6.7 percent (P<0.001) following the commencing of direct observation of treatment, and the occurrence of acquired resistance had turned down from 14.0 percent to 2.1 percent (P<0.001). The relapse rate had lessened from 20.9 percent to 5.5 percent (P<0.001), and the total number of relapses with multidrug-resistant pathogens had also reduced from 25 to 5 (P<0.001). The initiation of treatment for M. tuberculosis infection under direct observation had shown the way to noteworthy diminutions in the occurrence of primary drug resistance, acquired drug resistance, and relapse [31].

The results of this study conducted in Mulago hospital Uganda in 2005 , were early 'primary' drug resistance to streptomycin 39(28.3%) and Ethambutol 29 (21%) is very high [33], which is quite similar to the study executed by Sunil et al [28]at Gujarat city of India. The only difference was that the Primary Drug resistance to INH and Streptomycin was higher in Gujarat city rather than Ethambutol. The Primary drug resistance rate to Streptomycin and Ethambutol was sky high in Mulago Hospital Uganda as compared to the study done by Sunil et al [28]. This may be because poverty, lack of education, poor nutritional status and most importantly lacking DOT approach in these parts of the world, which actually needs great attention. Furthermore, Primary Drug resistance TB has been discussed in various other studies from different parts of the world [34, 35, 36] and all are in search of the occurrence and prevention of this grave variety of TB. Newer drugs for tuberculosis are impossible to come up in the near upcoming, though two classes (nitroimidazoles and oxazolidinones) and two drugs (bedaquiline and SQ-109) have new mechanisms of action for tuberculosis is under Phase II Trial. Accelerated approval was recently granted by the Food and Drug Administration for the use of bedaquiline in multidrug resistant tuberculosis [37]. All the authors are of the opinions that correct drug resistance scrutiny data can be used to judge and get better countrywide tuberculosis programs. Directly observed treatment Short Course therapy (DOTS) for tuberculosis should be started properly under proper supervision because an excellent result in reducing the rates of primary and acquired drug resistance have been reported and relapse amongst patients with tuberculosis with DOTS because DOTS is an international strategy to control TB [38].

CONCLUSION:

Primary Drug resistance to Mycobacterium tuberculosis results from unplanned and accidental mutations in the bacterial chromosome that results in condensed vulnerability to unambiguous agents. There is no confirmation that acquired genes or plasmids play a role in the coming out of antimicrobial resistance in mycobacterium. Even though phenotypic resistance has been documented for decades, the genotypic origin of drug resistance has simply been examined in nearby years. There is elevated prevalence of primary resistance against streptomycin, INH and Ethambutol, but fortunately Primary multi-drug resistance TB cases are frequently low in our country Pakistan as compared to Primary drug mono-resistance and poly-resistance resistance TB Cases. Primary drug resistance to at least solitary anti-tuberculosis drug was 11.5%. A new survey should be needed and should be conducted urgently in Pakistan because now new molecular diagnostics have made earlier and improved diagnosis of active disease possible. Laboratory expertise and resources are required for these tests to become available throughout the country. New vaccines against tuberculosis in advanced clinical trials offer hope for future tuberculosis control. There is a burning need to appraise countrywide primary resistance prototype so that policy in the management of tuberculosis be premeditated particularly for the use of management of TB. Confidence on DOT is also a most important point in the prevention of resistance and for achieving victorious results. Newer

drugs for tuberculosis are improbable to come up in the near future. Therefore, the input to achievement leftovers is satisfactory case finding, without delay and accurate diagnosis and efficient management of infective patients together with cautious introduction of second-line drugs to which the patient is susceptible.

TABLE I: DRUG RESISTANT TB DEFINITIONS

Term	**Definition**
Drug-Resistant TB	Generic term used to describe a TB strain resistant to one or more antituberculous drugs; most commonly refers to MDR-TB or XDR-TB
Mono-Resistance	Strains resistant to one of five first-line drugs
Poly-Resistance	Strains resistant to two or more drugs but not Both INH and Rifampicin
Multidrug-Resistant (MDR)	Strains resistant to both INH and Rifampicin
Extensively Drug-Resistant (XDR)	Strains resistant to both INH and Rifampicin, a flouroquinolone and at least one second-line injectable drugs(Amikacin,Kenamycin,Capreomycine,Viomycine)[3]
Totally Drug-Resistant Tuberculosis (TDR-TB)	Strains of Mycobacterium Tuberculosis that are resistant to every first and second-line TB drugs

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