Review on Mechanisms of Drug Resistance in Mycobacterium Tuberculosis

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Abstract: The resistance of certain mycobacterial tuberculosis strains to antituberculosis drugs is not a new phenomenon. It was noted when streptomycin was first used as monotherapy in the 1940s. Tuberculosis is becoming a worldwide problem due to the reoccurrence of the disease, the appearance of drug resistant strains, and the association of tuberculosis with other factors. The major objectives of the review is to indicate the mechanisms of drug resistance in mycobacterium tuberculosis infection, to show some of the factors that contribute for the development of antimycobacterial tuberculosis drug resistance and to highlight public health and economic impacts of antimycobacterial tuberculosis drug resistance. Drug resistance in mycobacterium tuberculosis may be intrinsic or acquired. Intrinsic resistance has been attributed to its cell wall properties, including the presence of mycolic acids, beta-lactamase enzymes and more recently, the role of efflux mechanisms have been recognized as an important factor in the natural resistance of mycobacteria against antibiotics. Acquired drug resistance in mycobacterium tuberculosis is caused mainly by spontaneous mutations in chromosomal genes, and the selective growth of such drug resistant mutants may be promoted during suboptimal drug therapy. The emergence of multidrug resistant tuberculosis that is mycobacterium tuberculosis strains, resistant to at least isoniazid and rifampicin is of great concern, because it requires the use of second line drugs that are difficult to procure and are much more toxic and expensive than the first line regimens. The global increase in drug resistance, particularly multidrug resistance tuberculosis, reflects at least in part, inappropriate use of antituberculosis drugs during the treatment course of patients. Additional factors such as age, HIV infection and socio-economic factors have been associated with development of drug resistant tuberculosis. Adult mortality due to age related development of antimycobacterial tuberculosis drug resistance has a significant effect on national economies. Multidrug regimens and prolonged treatment are required to reduce the development of drug resistance in mycobacterium tuberculosis infection.

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1.INTRODUCTION

The resistance of certain mycobacterial tuberculosis strains to anti-tuberculosis drugs is not a new phenomenon.It was noted when streptomycin was first used as monotherapy for TB in the 1940s. The development of multidrug treatment regimens in the 1950s offered a way to overcome the problem.From the 1950s through 1980s the frequency of the transmission of drug resistant organisms was thought to be low.It was not until the early 1990s when outbreaks of multi-drug resistant were reported in patients with HIV infection in the United States and Europe, and the problem received international attention (Jereb *et al*., 1993). Tuberculosis(TB) is becoming a worldwide problem due to the reoccurrence of the disease, the appearance of drug resistant strains, and the association of TB with other infectious agents (WHO, 2009).

Drug resistance in mycobacterium tuberculosis arises from spontaneous chromosomal mutations at low frequency. Clinical drug resistance TB largely occurs as a result of man –made selection of drugs during diseases treatment of the genetic alterations through erratic drug supply,suboptimal physician prescription and poor patient adherence (Zhang and Yew, 2009).Mutation and antibiotic selection of the resistant mutant are the molecular basis for resistance to streptomycin(ribosomal mutation), quinolones (gyrase or topoisomerase IV gene mutation) and rifampicin (RNA polymerase gene mutation).This mechanism underlies all drug resistance in mycobacterium TB (Bruntone*t al*., 2005). Additional factors such as previous treatment, HIV infection, age and socio-economic factors have been shown to be associated with increased occurrence of drug resistant TB (faustini *et al*., 2006).The emergence of multidrug resistant tuberculosis (MDR-TB), i.e. mycobacterium TB strains resistant to at least isoniazid and rifampicin, is of great concern, because it requires the use of second line drugs that are difficult to procure and are much more toxic and expensive than the first line drugs (Espanal *et al*., 2001).The rapid spread of drug resistance especially multidrug resistant TB (MDR-TB) and currently expensively drug resistant TB

(XDR-TB), both in new and previously treated cases, adds urgency to the need for decisive action for reduction measures(WHO, 2006).

Drug resistance has a major impact on the treatment success of TB.While standardized first line treatment is highly effective in drug susceptible TB,the treatment of multidrug resistant TB requires the use of second line drugs that are less effective,more expensive and often associated with severe side effects (Johnson, 2009).Adult mortality due to age related development of antimycobacterial TB drug resistance has a significant effect on national economies, both through the direct loss of productivity among those working age and by altering fertility, incentives for risk taking behavior and investment in human and physical capital (Corbett and Watt, 2003).Multidrug regimens and prolonged treatment are required to reduce the development of drug resistance in mycobacterium TB infection (Murry *et al*., 2002).Combination antibiotics into a single pill makes it less likely that you will miss taking any doses and failure to take a medicine which could prolong your treatment and increase your chance of developing drug resistant tuberculosis (Chiranjib *et al*., 2009).Therefore, the objectives of this review are to indicate the mechanisms of drug resistance in mycobacterium tuberculosis infection, to show some of the factors that contribute for the development of antimycobacterial tuberculosis drug resistance and to highlight impacts of drug resistance due to mycobacterium tuberculosis infection.

2.SOME BASIC CONCEPTS IN THE DEVELOPMENT OF DRUG RESISTANCE TO MYCOBACTERIUM TUBERCULOSIS INFECTION

Drug resistant TB is not a recent phenomenon. Mycobacterium TB strains that were resistant to streptomycin appeared soon after the introduction of drug treatment of TB in 1944 (Caminero, 2005).Drug resistance may be intrinsic or acquired. Intrinsic resistance in mycobacterium TB has been attributed to its cell wall properties, including the presence of mycolic acids, which are high molecular weight alpha-alkyl, beta-hydroxyl fatty acids covalently attached to arabinogalactan, and which constitute a very hydrophobic barrier responsible for resistance to certain antibiotics. In addition mycobacterium TB possesses beta-lactamase enzymes, which confer intrinsic resistance to beta-lactam antibiotics (Karakousis, 2004). Intrinsic drug resistance of mycobacterium TB has been attributed to the unusual structure of its mycolic acid-containing cell wall that gives the bacteria a low permeability for many compounds such as antibiotics and other chemotherapeutic agents (Jarlier and Nikaido, 1994). More recently, the role of efflux mechanisms has been recognized as an important in the natural resistance of mycobacteria against antibiotics such as fluoroquinolones and amino glycosides. Intrinsic resistance is thus important since it limits the number of drugs available for treatment and favors the emergence of strains with a high level of drug resistance (De Rossi and Riccardi, 2006).

Acquired drug resistance in mycobacterium TB is caused mainly spontaneous mutation in chromosomal genes, and the selective growth of such drug resistant mutants may be promoted during suboptimal drug therapy (Kolyava and Karakousis, 2012).Mutations to antimycobacterial TB drug resistance occurs at a rate of about one mutation every 10^{-8} cell divisions. Amplification of the genetic mutations through human error results in clinically drug resistant TB. These include monotherapy due to irregular drug supply, inappropriate doctor prescription and, most importantly, poor patient adherence to treatment (Zhang and Yew, 2009).Acquired resistance occurs in patients who have been treated in the past, and it is usually is a result of non-adherence to the recommended regimen or incorrect prescribing. It has been estimated that one in seven cases of TB is resistance to drugs that previously cured the diseases resistance arises when patients fail to complete their drug therapy, lasting six months or longer. The hardest TB bacteria are allowed to survive as a result, and as they multiply, they spread their genes to a new generation of bacteria and to new victims(Chiranjib *et al*., 2009). Unlike the situations in other bacteria where acquired drug resistance is generally mediated through horizontal transfer by mobile genetic elements, such as plasmids, transposons or integrons, in mycobacterium TB,acquired drug resistance is caused mainly by spontaneous mutations in chromosomal genes, producing the selection of resistant strains during suboptimal drug therapy(Kochi *et al*., 1993).

3. MECHANISMS OF RESISTANCE TO ANTI-MYCOBACTERIUM TUBERCULOSIS DRUGS

3.1. Mechanisms of resistance to first line agents

Currently, there are 10 drugs approved by the United States Food and Drug Administration (FDA) for treating TB. Of the approved drugs isoniazid, rifampicin, pyrazinamide and ethambutol are considered first line anti-TB drugs and form the core of initial treatment regimens (CDC, 2003).

3.1.1. Isoniazid

Isoniazid is the most widely used first line anti-TB drug. Since its discovery in 1952, isoniazid has been the corner stone of all effective regimens for the treatment of TB diseases and latent infection. The primary target of isoniazid inhibition is thought to be

the inhA enzyme (enoyl-acyl carrier protein reductase), involved in elongation of fatty acids in mycolic acid synthesis (Zhang and Yew, 2009).

Resistance to isoniazid occurs more frequently than for most anti-TB drugs; mutations in katG are the main mechanism of isoniazid resistance. Resistance to this drug also occurs by mutation in the promoter region of inhA operon, causing over expression of inhA, or by mutation at the inhA active site, lowering inhA affinity to the isoniazid. Mutations in the inhA not only cause isoniazid resistance, it also confers cross-resistance to the structurally related drug, ethionamide (Zhang and Yew, 2009).There are two mechanisms of acquired resistance to isoniazid which have been proposed. The first suggests that mutations in the katG gene inhibit the metabolism of isoniazid into an active form which inhibits an essential protein, inhA, in mycobacteria. Mutation in gene inhA can also confers isoniazid resistance by reducing affinity of isoniazid metabolic by products for inhA (Hugo and Russel, 1998).Most isoniazid resistant strains have amino acid changes in either the catalase-peroxidase gene (katG) or the promotor of a two gene locus known as inhA. Missense mutations or deletion of katG is also associated with reduced catalase and peroxidase activity (Fauci et al., 2008).

3.1.2. Rifampicin

The target of rifampicin in mycobacterium TB is the beta-subunit of RNA polymerase, where it binds and inhibits the elongation of messenger RNA (Blanchard, 1996).The great majority of mycobacterium TB clinical isolates resistant to rifampicin show mutations in the gene rpoB that encodes the beta-subunit of RNA polymerase. This results in conformational changes that determine a low affinity for the drug and consequently the development of resistance (Telenti *et al*., 1993). Resistance to rifampicin arises from mutations in the beta-subunits of RNA polymerase encoded by rpoB and resistant isolates show decreased growth rates (Denyer *et al*., 2004).Cross-resistance between rifampicin and other rifamycins do exist; an important finding related to resistance to rifampicin is that almost all rifampicin resistant strains also show resistance to other drugs, particularly isoniazid(Cavusoglu *et al*., 2004).

3.1.3. Pyrazinamide

Pyrazinamide is an important first line drug used along with isoniazid and rifampicin. It is a prodrug that requires conversion to its active form, pyrazinoic acid (POA), by pyrazinamidase/nicotinamidase enzyme encoded by the pncA gene of mycobacterium TB.Pyrazinamide resistant mycobacterium TB strains lose pyrazinamidase/nicotinamidase activity. The pncA mutations are highly diverse and scattered along the gene, which is unique to pyrazinamide resistance. Pyrazinamide is only active against mycobacterium TB at acidic PH where pyrazinoic acid accumulates in the cytoplasm due to an ineffective efflux pump. Pyrazinamide resistance was shown to be strongly associated with multidrug resistant TB and therefore, it was concluded that pyrazinamide should not be relied upon in managing patients with multidrug resistant TB as pyrazinamide resistant isolates had diverse nucleotide changes scattered throughout the pncA gene (Zhang and Yew, 2009).

3.1.4. Ethambutol

Ethambutol, a first line drug, is used in combination with other drugs and is specific to the mycobacteria. It inhibits arabinosyl transferase (embB) involved in cell wall biosynthesis (Johnson *et al*., 2009). In mycobacterium TB, embB is organized into an operon with embC and embA in the order embCAB. Mutations in the embCAB operon, in particular embB, and occasionally embC, are responsible for resistant to ethambutol. embC, embB and embA share over 65% amino acid identity with each other and are predicted to encode transmembrane proteins. It was found that mutations leading to certain amino acid changes are indeed causing ethambutol resistance while other amino acid substitutions have little effect on ethambutol resistance (Zhang and Yew, 2009).A genetic explanation of ethambutol resistance is mutation in embCAB gene cluster. More recently the inhibition of glucose conversion into the precursors used for the synthesis of cell wall polysaccharides has been proposed (Bhowmik *et al*., 2009).

3.2. Mechanisms of resistance to second line agents

Second line anti-TB drugs are inherently more toxic and less effective than first line drugs. They are mostly used in the treatment of multidrug resistant TB which is resistant to at least the two most important first line drugs, isoniazid and rifampicin, and as a result prolong the total treatment time (CDC, 2003).

3.2.1. Aminoglycosides (streptomycin, kanamycin /amikacin/ capreomycin)

Streptomycin

Streptomycin is an amino glycoside antibiotic that is active against a variety of bacterial species, including mycobacterium tuberculosis.It was formerly considered to be a first line agent and, in some instances, is still used in the initial treatment; however, an increasing prevalence of resistance to streptomycin in many parts of the world has decreased its overall usefulness (CDC, 2003).Streptomycin inhibits protein synthesis by binding to the 30s subunit of bacterial ribosome, causing misreading of the mRNA message during translation. The site of action of streptomycin is the 30s subunit of the ribosome at the ribosomal protein s12 and 16s rRNA.Resistance to streptomycin is caused by mutations in the s12 proteins encoded by rpsL gene and 16s rRNA encoded by rrs

gene .Mutations in rpsL and rrs are the major mechanisms of streptomycin resistance, accounting for respectively about 50% and 20% of streptomycin resistant strains.The most common mutation in rpsL is a substitution in codon 43 from lysine to arginine, causing high level resistance to streptomycin. Mutations of the rrs gene occur in the loops of the 16s rRNA and are clustered in two regions around nucleotides 530 and 915 (Zhang and Yew, 2009).

Kanamycine and Amikacin

Kanamycin and its derivative amikacin are also inhibitors of protein synthesis through modification of ribosomal structures at the 16s RNA. Mutations at the 16s RNA (rrs) position are associated with high level resistance to kanamycin and amikacin (Zhang and Yew, 2009).

Capreomycin

Capreomycin is a polypeptide antibiotic. A gene called tlyA encoding rRNA methyltransferase was shown to be involved in resistance to Capreomycin.The rRNA methyltransferase modifies the nucleotide C1409 in helix 44 of 16s rRNA and nucleotide C1920 in helix 69 of 23s RNA. Variable cross resistance may be observed between kanamycin, amikacin and Capreomycin. Multiple mutations may occur in the rrs gene in one strain, conferring cross resistance among these agents(Zhang and Yew, 2009).

3.2.2. Fluoroquinolones (ciproflaxan and oxfloxan)

In most bacterial species, fluoroquinolones inhibit DNA gyrase (topoisomerase two and topoisomerase four), resulting in microbial death. DNA topoisomerases are a diverse set of essential enzymes responsible for maintaining chromosomes in an appropriate topological state. In the cell topoisomerases regulate DNA super coiling and unlink tangled nucleic acid strands to meet replicative and transcriptional needs. DNA gyrase is a tetrameric A2B2 protein. The A subunit carries the breakage – reunion active site, where as the B subunit promotes adenosine triphosphate hydrolysis. Mycobacterium TB has respectively gyr A and gyr B encoding the A and B subunits. A conserved region, the quinolone-resistance-determining region (QRDR) of gyr A and gyr B, has been found to be a most important area involved in the exhibition of fluoroquinolones resistance in mycobacterium TB (Zhang and Yew,2009). Mutations within the QRDR of gyr A have been identified in clinical and laboratory selected isolates of mycobacterium TB, largely clustered at codons 90, 91, 94 and gyr B mutations appear to be of much rare occurrence. Generally, two mutations in gyr A plus gyr B are required for the development of higher levels of resistance (Takiff *et al*., 1994). Other mechanisms responsible for the mycobacterial resistance to fluoroquinolones, such as decreased cell wall permeability to drug, drug efflux pump or drug inactivation. Recently, a new mechanism of quinolone resistance mediated by MfpA was identified. MfpA is a member of the pentapeptide family of proteins from mycobacterium TB, whose expression causes resistance to fluoroquinolone drugs. MfpA binds to DNA gyrase and inhibits its activity in the form of a DNA mimicry, which explains its inhibitory effect on DNA gyrase and quinolone resistance. The alternative mechanisms accounting for mycobacterium TB resistance to fluoroquinolones are likely associated with lower levels of resistance, unlike that due to gyr mutations. However, when this alternative mechanisms co-exist with gyr mutations, the displayed resistance can be anticipated to be considerable (Zhang and Yew, 2009).

Table 1: Mechanisms of drug resistance in mycobacterium TB

Drug	Gene(s) involved in resistance	Gene function	Mechanism of action	Mutation frequency (%)
isoniazid	KatG inhA	Catalase-peroxidase Enoyl-ACP reductase	Inhibition of mycolic acid biosynthesis and other multiple effects	50-95 8-43
rifampicin	rpoB	Beta-subunit of RNA polymerase	Inhibition of RNA synthesis	95
pyrazinamide	pncA	Nicotinamidase/pyrazinamidase	Deletion of membrane energy	72-97
ethambutol	embB	Arabinosyl transferase	Inhibition of arabino-galactan synthesis	47-65
streptomycin	rpsL rrs gidB	S12 ribosomal protein 16s rRNA rRNA methyltransferase	Inhibition of protein synthesis	52-59 8-21 _
quinolones	gyrA gyrB	DNA gyrase subunitA DNA gyrase subunitB	Inhibtion of DNA gyrase	75-94

ACP = acyl carrier protein (Zhang and Yew, 2009)

4. RISK FACTORS FOR THE DEVELOPMENT OF DRUG RESISTANCE IN MYCOBACTERIUM TUBERCULOSIS INFECTION

4.1. Previous treatment

Previous treatment is an important risk factor for inducing drug resistance (especially MDR-TB). High resistance levels are expected among previously treated cases because drug resistance is a strong risk factor for recurrent tuberculosis. There are different explanations for inadequate treatment and development of drug resistance which may be due to inappropriate chemotherapy regimens, inadequate or irregular drug supply, unsatisfactory patients or clinician compliance, lack of supervision of treatment and absence of infection control measures in hospitals (Salih and Merza, 2010). The factors related to previous treatment include incomplete and inadequate treatment. Many new cases of MDR-TB are created each year by physician's errors (errors in choice of drugs, dosing intervals, duration). Some other factors also play important role in the development of MDR-TB such as poor administrative control on purchase and distribution of drugs with no proper mechanisms on quality control (Iseman, 1993).

Patients have been allowed to take their medications at home completely unsupervised. There is a danger that if the patient is sent home with three separate drugs, he or she might take a single drug at a time. In the patient with extensive lung disease taking a single drug just a few days may allow drug resistance to emerge. If a patient happens to be resistant to one drug and takes a combination of two drugs including the one to which he or she is resistant, drug resistance to the second drug will emerge. Similarly if the patient is resistant to two drugs, and takes these two drugs and a third drug only then resistance to the third drug will emerge and so on (Toungoussova, 2001).

4.2. HIV infection

The HIV and TB epidemics not only co-exist in most parts of the world today, but are synergistic. In individuals latently infected with mycobacterium TB, HIV co-infection is estimated to increase the risk of progression to active TB by 50 fold on a yearly basis compared with those who are not infected with HIV. The risk in these co-infected individuals of activating their mycobacterium TB infections appears to correlate with their degree of suppression of cellular immunity as measured by CD4+ cell counts. Treatment of TB in AIDS patients is complicated by drug-drug interactions between antiretroviral agents and anti-TB agents. The most significant result of these interactions is that anti-TB drugs decrease the serum half-lives of these antiretroviral agents (Ma *et al*., 2007). HIV-positive people are especially likely to develop active TB, and drug resistant forms of the disease are especially dangerous for them. What is more, the most powerful AIDS drugs (antiretroviral therapy) interact with rifampicin and other drugs other drugs used to treat TB, reducing the effectiveness of both types of medications. To avoid interactions, people living with both HIV and TB may stop taking antiretroviral therapy while they complete a short course of TB therapy that includes rifampicin or they may be treated with a TB regimen in which rifampicin is replaced with other drugs that is less likely to interfere with AIDS medications. In such cases, doctors carefully monitor the response to therapy, and the duration and type of regimen may change over time (Chiranjib et al., 2009). HIV infection is not an independent risk factor for the development of MDR-TB. However, it has been shown to influence MDR-TB by favoring the risk transmission of multidrug resistant strains of mycobacterium TB (Salih and Merza, 2010).

4.3. Age

Tuberculosis is more common in elderly persons (above age 65).Many elderly patients developed the infection some years ago when the disease was more wide spread. There are additional reasons for the vulnerability of older people; those living in nursing homes and similar facilities are in close contact with others who may be infected. The aging process itself may weaken the body's immune system, which is then less able to ward off the tubercle bacillus. Finally, bacteria that have lain dormant for some time in elderly persons may be reactivated and cause illness (Bhwmik *et al*., 2009).

4.4. Socio-economic factors

Socio-economic factors for the development of anti-tuberculosis drug resistance include drug abuse, poverty and homelessness that may induce treatment failure and subsequently emergence of drug resistance TB (Salih and Merza, 2010). Poor life style and financially not able to purchase the medicines and carry on treatment. Considering TB a havoc and afraid of disease itself along with social isolation and attitudes of the society. Treatment prolongation also increases cost to the patient because transport adds to the expense of the patient who had to come for follow up visits at the hospital (Saira zai *et al*., 2010).

4.5. Contact with a person having infectious drug resistant tuberculosis

Contact with a person, who has infectious, drug resistant TB is a significant factor for primary resistance (intrinsic resistance). Recent nosocomial outbreaks demonstrate a strong correlation between previous exposure to a patient who has infectious,

multidrug resistant TB and the subsequent development in the contact of multidrug resistant TB .Several factors are the infectiousness of the possible source; the closeness and intensity of exposure and the contact's likelihood of exposure to persons with drug susceptible TB. Any person who shares the air space with a patient with multidrug resistant TB for a relatively prolonged time (e.g., household member, hospital roommate) is at high risk for infection than those with a brief exposure to multidrug resistant TB patients, such as a onetime hospital visitor. Exposure of any length in a small, enclosed, poorly ventilated area is more likely to result in transmission than exposure in large, well-ventilated space. Exposure during cough inducing procedures (e.g., broncoscopy, endotrachial intubation, sputum induction, and administration of aerosol therapy) may greatly enhance drug resistant TB transmission (Toungoussova, 2001).

5. IMPACTS OF ANTI-MYCOBACTERIAL TUBERCULOSIS DRUG RESISTANCE ON PUBLIC HEALTH AND ECONOMY

5.1. Public health impacts

The emergence of resistance to drugs used to treat TB, and particularly MDR-TB, has become a significant public health problem in a number of countries. The first impact of the discovery of MDR-TB in patients is the need to recognize that all TB patients have the potential of being multidrug resistant. A combination contributing factors has lead to the current public health crisis; a failing national TB program, denial and lack of compliance on the part of patient, lack of regulations of Doctors on private practices. Governmental policy failure and corruption, social and economic problems and a growing HIV epidemic. This situation must be combated on several fronts including seeking global aid, implementing DOTS and non –DOTS and HIV programmes enactive regulatory legislation and establishing continuing medical education programs among private practitioners (Saira zai *et al*., 2010).

5.2. Economic impacts

The costs of multidrug resistant TB (MDR-TB) reach far beyond the cost of the clinical treatment of the patient. The cost to the larger economy includes lost productivity and lost tax revenue to the state as well as the cost of supporting the family if the patient is in the breadwinner. Infected persons indirectly affect the economy due to long term disability at work places and increased risk of transmission infection to the people in the surrounding (Saira zai *et al*., 2010). The greatest burden of TB falls on productive adults who, once infected, are weakened and often unable to work. The burden of taking care of sick individuals usually falls to other family members and, in addition to put them at greater risk of infection, and can lower their productivity (Russel, 2004).

6. METHODS APPLIED TO REDUCE ANTI-MYCOBACTERIAL TUBERCULOSIS DRUG RESISTANCE

6.1. Ensure Accessibility of drugs

Multiple drug therapy to treat TB means taking several different antibiotics at the same time. This is the first choice of treatment for TB that is growing on your body. Most of these medicines are given as pills. The standard treatment is to take isoniazid, rifampicin, ethambutol and pyrazinamide for two months. Treatment is then continued for at least four months with fewer medicines. Combining antibiotics helps to reduce the chance of developing drug resistant TB (Chiranjib *et al*., 2009). Successful therapy requires the prevention of the emergence of drug resistant strains by the simultaneous use of at least two drugs to which the organism is sensitive (Greenwood *et al*.,2007).

6.2. Avoid self-Medication

Stopping treatment too soon or skipping doses can allow the bacteria that are still alive to become resistant to those drugs, leading to TB that is much more dangerous and difficult to treat. Drug resistant strains of TB can quickly become fatal, especially if your immune system is impaired. In an effort to help people sick with their treatment, a program called directly observed therapy (DOT) is recommended. In this approach, a nurse or other health care professional administers your medication so that you do not have to remember to take it on your own. If you take by yourself, after a few weeks you won't be contagious and you may start to feel better. It might be tempting to stop taking your TB drugs. When you stop treatment early or skip doses, TB bacteria have a chance to develop mutations that allow them to survive the most potent TB drugs. The resulting drug resistant strains are much more deadly and difficult to treat. To avoid this sometimes clinics provide incentives, such as food coupons or transportations, for people to show up for their appointments (Bhowmik *et al*., 2009).

6.3. Follow standardized regimens

The choice by each country of a limited number of standardized regimens should be based on the availability of financial resources, efficacy, effectiveness and applicability in the current health system, population distribution and morbidity. Standardized regimens have the following advantages over individualized prescription of drugs:- reduces errors in prescription there by reducing the risk of development of drug resistance, facilitates of drug

needs, purchasing, distribution and monitoring, facilitates staff training and reduces costs. Treatment regimens should consist of at least four drugs with either certain, or almost certain, effectiveness. Where evidence about the effectiveness of a certain drug is unclear, the drug can be part of the regimen but it should not be depend upon for success. Often, more than four drugs may start if the susceptible pattern is unknown or the effectiveness of one or more agents is questionable (WHO, 2003).

6.4. Avoid substandard medication

Anti-tuberculosis chemotherapy is designed to kill tubercle bacilli rapidly, minimize the potential for the organisms to develop drug resistance and sterilize the host's tissues. The achievement of these requires that a combination of agents with specific activities be administered for a sufficiently long period of time. As a consequence of these effects, the patient is cured and has only as small likelihood of relapse. Treatment for a defined duration without accounting for the number of doses taken can result in undertreatment. Therefore, the determination of whether or not treatment has been completed is based on the total number of doses taken not only the duration of the therapy (CDC, 2003).

6.5. Patient education

Educating patients about TB disease helps to ensure their successful completion of therapy. Health care providers must take the time to explain clearly to patients what medication should be taken, how much, how often, and when. Patients should be clearly informed about possible adverse reactions to the medications they are taking and when to seek necessary medical attention. Providing patients with the knowledge they need regarding the consequences of not taking their medicine correctly is very important (CDC, 2003).

6.6. Follow clear and legible prescription writing

Prescription is a written order of a registered physician to the pharmacist with directions for the preparation of the prescribed drugs, and their use by the patient. It is the focal point in the physician-patient-pharmacist relationship which serves as a communication between the physician and the pharmacist, both of share the responsibility of safeguarding the patient. A valid prescription should invariably be written and signed by the prescriber (Barar, 1985).

7. CONCLUSIONS

Tuberculosis is becoming a worldwide problem due to the reoccurrence of the disease, the appearance of drug resistant strains and the association of tuberculosis with other infectious agents.Drug resistance in mycobacterium tuberculosis arises from spontaneous chromosomal mutations at low frequency. Clinically drug resistance tuberculosis largely occurs as a result of man-made selection of drugs during disease treatment of these genetic alterations through erratic drug supply, suboptimal physician prescription poor adherence. Additional factors such as age, HIV infection, previous treatment and socio-economic factors have been shown to be associated with increased occurrence of drug resistance tuberculosis.Drug resistance has a major impact on the treatment success of TB. Adult mortality due to age related development of antimycobacterial TB drug resistance has a significant effect on national economies, both through the direct loss of productivity among those working age and altering fertility, incentives for risk taking behavior.Multiple drugs are necessary for the treatment of tuberculosis. Although standardized first line drugs are highly effective in drug susceptible strains, treatment of multidrug resistant TB requires the use of second line anti-TB drugs. Therefore, it is highly recommended to strictly follow the appropriate treatment guidelines to ensure adequate success rate of treatment in drug susceptible and drug resistant strains; treatment of TB should be based on different case categories administered under direct supervision to reduce non-compliance and development of drug resistance.

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