Multi-dug resistance in pulmonary tuberculosis : global and local problem

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Tuberculosis is an ancient, serious disease, accounting to 26% of all preventable adult deaths globally. Now, WHO estimated that 8 million new cases of tuberculosis -occurs worldwide annually, of them 3 million die.After introduction of anti tuberculosis drugs in the middle of 20th century, marked improvements and advances in drug therapy of tuberculosis had occurred so that morbidity and mortality of this serious disease were consequently lowered. Despite these improvements, there was a slowly growing problem that developed from the beginning of anti- tuberculosis drug therapy which now constitutes a real threat and a challenge to world public health. This problem was the development of drug -resistance by the bacilli to the individual drugs used in treatment (mono resistance). Initially, this was overcome by multiple drug regimens especially those including potent sterilizing drugs like Isoniazid and Rifampicin.Due to many factors related to the patients, their managing physicians or the drugs themselves, resistance developed also to the most potent drugsused in treatment (i.e. Isoniazid and Rifampicin) further complicating the problem development on new generations of the bacilli which are multi- drug resistant.Second line drugs which are more expensive and (importantly) more toxic were used to overcome resistance to the cheap, more potent 1st line drugs but the problem is increasing as resistance to 2nd line drugs also developed with the spread of such very serious generations of tubercle bacilli which are considered extensively drug resistant.Recent data showed that 13% of all new cases of tuberculosis have mono-resistance while 1.6% are multi-drug resistant and extensive drug- resistance is much lower. Although the incidence of multiple and extensive drug resistance is low, yet constitutes a medical challenge because treatment of such cases is very difficult and mortality is high.There are many factors that favor the development of drug resistance by TB bacilli which should be overcome when searching for a solution of drug resistance. These factors include selective pressure, gene mutations, gene transfer, and the improper use of anti-tuberculosis drugs.Resistance to anti-TB drugs is either primary (if the patient is infected by resistant organisms) or acquired (if resistance develops during treatment). The type of resistance is important epidemiologically while planning for local treatment programs.Also, from the epidemiologic point of view, developing new, rapid and accurate tests for detection of such resistance is of paramount importance. In the same way, efforts to have new effective drugs against TB considering the financial and cultural characteristics of a given

population are also epidemiologically very important.A data base information system is now available at WHO concerned with recording all known mutations and their characteristics and is open to add any new mutations that could be recorded in the future. This data base is very essential for guidance while trying to develop new anti-TB drugs and MDR-TB control campaigns.Understanding molecular mechanisms of development of drug resistance by TB is also essential when planning for new anti-TB drugs. Resistance to INH develops due to mutation in 4 genes called, KatG, inhA, Ndh and kas genes. KatG encodes for a peroxidase responsible for activation of INH into a toxic product inside the bacillus while inhA encodes for aprotein that makes a complex with INH and interferes with mycolic acid synthesis. Mutation in Ndh results in NAD oxidation with accumulation of NADH in bacterial cells with resultant interference with action of INH. Resistance to RIF is due to mutation in the b-subunit of RNA polymerase enzyme, the target of action of this important anti-TB drug. Resistance to EMB is due to mutations in 3 genes encoding for arabinosyl transferase iso-enzymes A, B and C while resistance to PZA is due to mutation in the pncA gene encoding for PZase enzyme responsible for activation of PZA into POA. Mutations in the genes encoding for gyrase enzymes (A and B) and named gyrA and gyrB are responsible for resistance to FQ which are recently used as anti-TB drugs. There are also many molecular mechanisms underlying resistance to the second line and injectable drugs.The usual policy of searching for resistance only when it is clinically suspected has resulted in development of more resistance, so this must be replaced by diagnosing drug resistance in TB patients before starting treatment. Conventional culture and sensitivity methods are cheap but time consuming. Recent rapid culture methods with molecular diagnosis of resistance using gene probing and amplification assays are sensitive,specific and take short time which are all very important determinants in managing such patients. The problem with these diagnostic methods is the high expense and sophisticated technical methods which are not available in many parts of the world. One recent method for early detection is the MODS assay. This assay depends on detection of micro- colonies of TB by microscopic examination of fluid culture media inoculated with patient samples. The low cost and striking short time for detection of drug sensitivity in this method (about7 days), makes it worthy for global wide application.Number of drugs to which the organism is resistant, use of injectable drugs, the immune status and co-operation of the patient and expertize of the managing team are detrimental factors in treatment of MDR patients. Current regimens for treating patients with known RIF sensitivity (or sensitivity status is unknown) is by INH+ RIF + S + ETB + PZA+ MXF+ DCS and omitting RIF if resistance to it is present. If organisms are resistant to both INH and RIF and sensitivities to other drugs are known,5 drugs of the following are chosen: an injectable aminoglycoside e.g. Kanamycin, PZA, EMB, a fluoroquinolone e.g. MXF, Rifabutin, DCS, a thionamide e.g. Prothionamide, a macrolide e.g. clarithromycine,linezolide, interferon-γ and thioridazine. Treatment must be under closesupervision and patients monitored by repeated culture and sensitivity testing on monthly basis for at least 18 months, as such patients are usually treated for more than 2 years.The role of surgery in management of MDR-TB patients has revived due to the limited resources of available treatments and their high failure rate. De-bulking of infected tissues or collapse therapy methods e.g.

thoracoplasty can be used. The current strategy favors early surgical intervention.Because of the limited number of effective and safe drugs for treatment of drug resistant TB, searching for new, safe, cheap and effective drugs is of paramount importance in overcoming the problem of MDR-TB. Fortunately many of such drugs are now in phase I and II trials.TMC-207 is a diarylquinoline compound with efficient killing of TB and has synergy with other drugs. Phase II trials are expected to be completed in 2011. PA-824 is a nitroimidazopyran which is highly effective against all types of TB even resistant organisms. Regimens including this drug cured rats infected with resistant TB in less than 2 months. The drug still in phase I trials. OPC-67683 is a nitroimidazole compound which is 20times more potent than PA-824 and very encouraging but still in phase II trials. LL-3858 and SQ-109 are drugs with new mechanisms of action that still in phase I trials.Treatment failure in MDR-TB cases is very high, so care must be exercised to minimize failure rate as possible by careful review of patient medical history, improving general conditions of the patients, treating associated medical conditions e.g. diabetes and HIV infection as well as close observation during the whole treatment course. In patients who fail to respond despite these extensive measures, treatment can be suspended but the patient should not be neglected and should have adequate medical and psychological support.Recently, nanotechnology has opened the door of a new era in medicine. Nano-medicine is very promising in management of many unsolved respiratory disorders; most important of them is -overcoming the problem of drug resistant TB. Labeled nano-robots, optical bio sensors, and colored nano-indicators are now under trials in diagnosing drug -resistant TB with very encouraging results. Giving anti-tuberculosis drugs in nano formulation both by inhalation and parenteral route proved very effective against TB in lab animals. Drugs given in nano-formulationshowed very high bioavailability and very long half-life even with the lowest doses, features that can greatly improve patient compliance and minimize treatment failures. Aerosolized, nano-formulated tuberculo- proteins provide an efficient and safe way for vaccination against TB and trials are now running in this way.WHO provided a program that could be the cornerstone for effective control of MDR-TB worldwide when implicated in national TB control plans. This program depends on a DOTS framework, sustained political commitment of local authorities in TB control programs, rational case finding strategy including accurate timely diagnosis through quality- assured culture and DST, appropriate treatment strategies that use second line drugs under proper case management conditions, uninterrupted supply of quality-assured anti-tuberculosis -drugs and standardized recording and reporting systems.Effective control of MDR TB requires effective case finding strategies through targeting risk groups for DST (e.g. close contacts, previously treated, HIV infected and pediatric patients), proper collection and processing of specimens, use of rapid methods for DST including second line drugs. Proper management of contacts by clinical, radiological andbacteriological means with chemoprophylaxis for non-infected individuals and optimal therapy for detected cases is a very important part of an effective control program.Worldwide, not all counties have accurate estimates of the prevalence ofMDR-TB but the overall trend is towards rising.In the region of Americas, more than 90% of smear positive TB cases were tested for drug resistance. Regular

surveys showed a steady state of low prevalence of drug resistance (1% among new, and 4% among previously treated cases) in Canada and decreasing prevalence in USA. All other countries in the region show generally low prevalence pattern except in Bolivia and Ecuador where resistance among new cases is around 5%.In Eastern Mediterranean Region, very limited surveys were done, so results were difficult to interpret but overall trend is rising with the lowest prevalences in the Gulf countries and the highest in occupied Palestine (Israel) as most people are immigrants from poor areas in the world with high prevalence in their native nations but new notifications are decreasing.In Africa, only Botswana, Sierra Leone and South Africa had carried out repeated surveys. In Botswana and South Africa, the notifications of drug resistant TB was doubled between 1995 and 2001while in Sierra Leone little rise occurred. Limited surveys in Democratic Republic of Congo showed a high prevalence and this appears to be the case in other African countries especially those of central Africa.The European region shows the greatest heterogeneity of resistance parameters in the world including both highest and lowest prevalences. In western and central European countries the overall MDR-TB is relatively low accounting for less than 1-2% of newly diagnosed cases. In Poland, although overall resistance is low, yet it has doubled in recent surveys. Contrary to western and central Europe, eastern European region shows high and steady rise in prevalence of MDR-TB between 1996 and 2001in most countries especially Estonia, Latvia, Lithuania, Kazakhstan, Uzbekistan and Tomsk and Ivanovo Oblasts in Russian Federation.In South-East Asian region, very limited surveys were done except in Thailand, some regions in India, Nepal and Myanmar with overall rise in MDR-TB among both of new and previously treated patients.In Western Pacific Region, surveys of MDR-TB were conducted regularly and frequently since early 1990s. The overall resistance in this region is very low especially in Japan, Singapore, Hong Kong, Australia and New Zealand.Overall, by 2007 there were 9.24 million MDR-TB cases in the globe, more than 80% of them were concentrated in only 22 high burden countries. India, China, Indonesia, Nigeria and South Africa have the highest burden in order. WHO put the Stop TB Strategy to reduce MDR- TB to the lowest figures possible by 2015 with the attention to such high burden countries.In Egypt no accurate surveys were done but according to WHO report in2008, MDR-TB in the country showed moderate prevalence among new cases (2.2%) with unusually high rate of RIF’s mono-resistance. Recentlynational attention to the problem of drug resistance has led to opening of many wards specialized in managing MDR-TB. At Alabbasya Chest Hospital, there is now a ward of two floors prepared for specialized care of such patients. One controlled study was carried out at this ward and68% success was obtained in 65 patients who completed scheduled treatment (of 168 enrolled). The striking observation in this study wasthat large number (61.3%) of patients not completed the treatment course and mortality rate was very high (17%). So, more efforts are needed to face this serious problem in our country.