RISK FACTORS FOR MULTI-DRUG RESISTANT TUBERCULOSIS: A REVIEW

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SUMMARY

The current review aims to determine the risk factors associated with multi-drugs resistant TB (MDR-TB). Previous treatment is the most important risk factor for inducing MDR-TB. Other important associated factors are: immigration, age 45-64 year, male sex, HIV infection, alcoholism, smoking, diabetes mellitus, and poor socio-economic factors. Effective treatment, control and prevention of emergence and transmission of drug-resistant TB are required in all countries. To achieve this, the World Health Organization (WHO) recommended the adoption of Directly Observed Therapy Short-Course (DOTS) programme which involves giving effective and regular anti-TB drug supply, government security and financing commitment, case detection and diagnosis by smear microscopy, and monitoring the performance and outcome. It is highly recommended to strictly follow the appropriate WHO treatment guidelines, to ensure adequate success rate of treatment in drug-susceptible and drug-resistant strains; this will limit emergence of resistant strains and prevent spread of the disease. The emergence of aggressive new forms of drug-resistant TB is worrying that requires reinforcement of control measures. This demands special attention to case detection and prompt treatment of MDR-TB, extensively drug resistant TB (XDR-TB), and totally drug resistant TB (TDR-TB) to prevent transmission of the disease and further development of drug-resistant strains beyond this stage.

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Key words: Risk factor, *Mycobacterium tuberculosis*, MDR-TB

Tuberculosis (TB) is a major, global public health problem, particularly in low- and middle-income countries. The total number of TB cases is still increasing worldwide, particularly in countries where HIV infection is epidemic. The recently published World Health Organization (WHO) report stated that there were 9.27 million new cases of TB in 2007, 1.8 million deaths from TB, and 13.7million prevalent cases.[1]

Recently Mycobacterium tuberculosis (MTB) has intensely been studied because of its resurgence and the emergence of drug resistant strains.[2,3] MDR-TB, that is MTB strains resistant to at least isoniazid (INH) and rifampicin (RIF), is present in all continents, with 0.5 million estimated new cases in 2007.[1] The highest proportion of MDR-TB cases has been reported from India, China, the Russian Federation, South Africa and Bangladesh.[1] MDR-TB poses a significant global and public health concern, because of low efficacy rates for first line treatment regimens, 18 to 24 months of treatment and association with considerable mortality worldwide.[4,5] An additional concern is the persistence of high or increasing incidence and spread of MDR-TB in industrialized and the developing world, related to poverty, migration, ethnic conflicts, substance abuse and the increase in HIV infection, sometimes coupled with the poor

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performance of national programmes. These factors may lead to the development or increase of MDR which, however, is susceptible to proper health control measures.[6] The measures are aimed at reducing the transmission through rapid identification of infectious patients and fast adequate diagnostic measures, followed by immediate treatment with effective drugs according to resistance, as long as sufficient protection by vaccination is not available.[7]

Recently, reports of MTB strains with extensively drug resistant TB (XDR-TB) strains have been described.[2,8] XDR-TB is defined as TB caused by MDR strains that are also resistant to a fluoroquinolones (FQs) and, at least, one second-line injectable agent (amikacin "AMK", kanamycin "KM" and/or capreomycin "CAP").[1] More recently report of MTB strains of totally drug resistant TB (TDR-TB) or super XDR-TB has been described.[9] TDR-TB is defined as MTB isolates resistant to all first line (INH, RMP, STM, ethambutol "EMB", and pyrazinamide "PZA"), and second line drugs (ofloxacin "OFX", ciprofloxacin "CIP", cycloserine "CYC", prothionamide "PTH", AMK, KM, ethionamide "ETH", para-aminosalicylic acid "PAS", and CAP).[9]

The aim of this review is to outline risk factors associated with MDR-TB, and the policies for countering the feasible ones.

Risk Factors Influencing Development of Drug Resistance:

Previous treatment It is an important risk factor for inducing drug resistance (especially MDR-TB).[6,10-15] Generally, high resistance levels are expected among previously treated cases because drug resistance is a strong risk factor for recurrent TB.[10] The WHO/IUATLD working group on global surveillance for anti-TB drug resistance reported a prevalence of primary MDR of 1.4% and acquired resistance of 13% in previously treated patients[16]. Therefore, prevalence of MDR-TB is 10 times higher in previously treated patients. The median combined prevalence of MDR-TB is 2.2%.[16] The high rate of acquired resistance is justified with previous inadequate treatment. There are different explanations for inadequate treatment. It may be due to inappropriate chemotherapy regimens, inadequate or irregular drug supply, unsatisfactory patients or clinicians compliance, lack of supervision of treatment and absence of infection control measures in hospitals.[6,10,17]

Immigration This has been documented as one factor leading to the increased resistance rate of TB in some countries.[11,18-20] Factors contributing to increased prevalence of drug resistance in immigrants are believed to be lack of access to health care services and inappropriate working and housing conditions. In certain studies,[21,22] risk of resistance to anti-TB drugs has been reported to be 3- to 10- folds higher in immigrant than non-immigrant population. In another study,[23] 50% of TB cases in immigrant population had isolates that were resistant to at least one of the standard five drugs, and almost 17% were MDR-TB.

Age Age has been found to be independently associated with drug resistance and there was significantly higher proportion of MDR-TB among the age group of 45-64 years.[15] Faustini et al. found that MDR-TB was more likely in patients under 65 years, but the association was weak and more heterogeneous in patients under 45.[24] Another study conducted by Espinal et al. found that MDR-TB were more prevalent among age group 35–64 years old.[25]

Sex There is no clear association between MDR-TB and sex; however, some studies have shown that male sex may act as significant risk factor for MDR.[26] It has been hypothesized that women are more compliant with treatment and therefore less likely to receive

inadequate treatment.[24] In contrary to MDR-TB patients, female gender has been found as a significant risk factor in XDR-TB patients; this was attributed to the delayed referral of female patients to hospitals because of certain social factors.[27] Further studies are recommended to better understand the role of gender in drug-resistant TB.

HIV HIV infection is not an independent risk factor for development of MDR-TB.[15,28] However, HIV infection has been shown to influences MDR-TB by favoring the risk of transmission of multidrug-resistant strains of MTB.[29-31]

Alcoholism It has been identified to enhance default and failure rates among new TB cases. Hence, it increases the rate of MDR-TB cases.[6,32-34]

Diabetes mellitus (DM) DM patients are prone to higher incidence of TB drug resistance.[34-36]

Socio-economic factors There are other socio-economic factors like drug abuse, poverty and homelessness that may induce treatment failure and subsequently emergence of drug resistance TB.[6,30-39]

MDR-TB, XDR-TB and TDR-TB: What to do?

According to Centre for Disease Control (CDC) and the WHO, a survey was conducted based on an international network of TB laboratories for year 2000 – 2004. The result showed that 20% and 2% of MTB isolates were MDR and XDR, respectively. Additionally it was reported that the total number and proportion of XDR-TB isolates observed worldwide (excluding South Korea) increased from 14 (5% of MDR-TB isolates) in 2000 to 34 (7% of MDR-TB isolates) in 2004.[40]

In order to reverse the increasing trend in drug-resistant TB, effective treatment, control and prevention of emergence and transmission of drug-resistant TB are required in all countries. The WHO recommended that the best way to prevent emergence of drug-resistant TB is to encourage adoption of Directly Observed Therapy Short-Course (DOTS) programme. The programme involves giving effective and regular anti-TB drug supply, government security and financing commitment, case detection and diagnosis by smear microscopy, and monitoring the performance and outcome.[41,42] Nevertheless, failure of treatment may occur due to many factors, resulting in emergence of MDR-TB. In the case of drug-resistant TB in general and MDR-TB in particular, the WHO established DOTS-Plus within the context of basic DOTS programme. The programme relies on quality-assured and internationally recommended treatment regimens administered under strict supervision that must be scaled up and strengthened to prevent spread of drug-resistant strains i.e. MDR-TB and XDR-TB. Strictly speaking the goal of DOTS-Plus is to prevent further development and spread of MDR-TB.[43] The emergence of MDR-TB strains is of great concern, because it requires the use of second line drugs that are less efficient, much more toxic and expensive than the first line regimen.[4] It is noteworthy that the lengthy treatment course of drug-resistant TB results in complexity and problematic treatment outcome. This can be explained by prolonged time of diagnosis, difficult adherence to treatment and some default from treatment. For these reasons, more aggressive form of drug resistant-TB emerges i.e. XDR-TB, TDR-TB. XDR-TB treatment is much more difficult and costly than MDR-TB. Furthermore, the treatment outcome is found to be significantly worse than that of other MDR-TB cases.[3,28,44]

Although drug-resistant TB (MDR-TB and XDR-TB) is a critical risk to patient life, yet treatment is feasible and cost effective if WHO guidelines are followed, with cure rates of up to 80% among multidrug-resistant cases and up to 60% among extensively drug-resistant cases in low-resource settings. Inappropriate treatment that is not in line with the recommended guidelines runs the

risk of raising mortality; increasing resistance and spreading resistance even further.[45]

The newly emerging form of drug-resistant TB strains (TDR-TB) is potentially untreatable since they are resistant to all first-line drugs and to the six second-line classes. TDR-TB constitutes a deadly threat to the affected patients because we do not know how to treat these patients and what kind of combination should we use[9] The current un-effective anti-TB drugs for such patients increase the complexity of the situation, and perplexing TB treatment 60 years back to the era before antibiotics.

Overall, XDR-TB[2,46] and TDR-TB[9] constitute an emerging threat for TB control and the further spread of drug resistance. It has been stated that drug-resistant TB is equally infectious as drug-susceptible TB.[47] One of the important factors that facilitate transmission of drug resistant TB is HIV infected patients; such patients have a rapid progressive course to fatal disease.[28] Therefore, drug-resistant TB patients co-infected with HIV should be diagnosed quickly and prompt combination treatment commenced.[48,49] This is important to prevent further transmission of drug-resistant strains. Finally, rapid detection of drug resistance to both first- and second line anti-TB drugs is a key component of TB control programs.

CONCLUSION

It is important to recognise the growing global challenges of TB as a result of current global resurgence of the disease and progress in emergence of drug-resistant TB i.e. MDR-TB, and especially XDR-TB and TDR-TB. Additionally, the drug-resistant TB and HIV association has increased the complexity of the situation. It is highly recommended to strictly follow the appropriate WHO treatment guidelines, to ensure adequate success rate of treatment in drug-susceptible and drug-resistant strains; this will limit emergence of resistant strains and prevent spread of the disease. The emergence of aggressive new forms of drug-resistant TB is worrying that requires reinforcement of control measures. This demands special attention to case detection and prompt treatment of MDR-TB, XDR-TB, and TDR-TB to prevent transmission of the disease and further development of drug-resistant strains beyond this stage. A prospective population-based surveillance encompassing all regions of the world is warranted with the implementation of standardized protocols to further understand trends of drug resistance.

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