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Editorial

TUBERCULOSIS MANAGEMENT-TIME FOR PARADIGM SHIFT?

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World Health Organisation (WHO) has published the fourth edition of *Treatment of tuberculosis:guidelines*.[1]It extensively covers various aspects of management of TB including emerging problems such as multidrug resistant-tuberculosis (MDR-TB) and HIV-TB co-infection.The inherent strength of the guidelines is the simplified manner of presentation, greatly benefitting readers to understand the key messages. There are many recommendations, which call for a radical change in existing treatment practices throughout the world. Majority of these recommendations are not based on sound evidence and are derived from common consensus, affected by individual believes and perception. Hence, these recommendations are not binding on the countries that choose not to implement them. Table 1 summarises salient recommendations and reasons to approve or disapprove the same.

There are potential areas of disagreement in the guidelines, requiring re-evaluation and further strengthening.Majority of the members constituting guidelines' group belong to countries with minority of TB cases and thus have limited experience of treating these patients. Besides, since most of these countries are rich in resources, respective authors may be unaware of challenges faced by resource constrained developing nations in executing the desired recommendations in a programmatic set up. There is minimal representation from South-East Asian countries that account for one third of global TB burden.[2]More participation from this part of the world would have facilitated decision making in areas of conflicts. At the same time, it would have addressed operational difficulties and ground realities in implementing the recommendations, thereby ensuring universal acceptance of the document.

In the new definition for definite case of TB, a patient with even one positive AFB smear is considered as a 'case' in countries having proper functional external quality assurance (EQA) system. The number of specimens has been reduced from three to two for screening of TB suspects, since the additional yield of third sputum smear is low (2 to 5%).[3]This approach decreases burden on laboratories and simultaneously helps in early initiation of treatment. Moreover, number of visits for collection of sample are reduced, thereby more convenient for the patients. However, this applies only when there is well functioning EQA with blind rechecking as well as good internal quality control helping to decrease false positive results. This is a significant limitation for resource limited settings, where ensuring quality control is not always feasible. Hence, this recommendation, if implemented blindly, may lead to transmission of disease, propagation of drug resistance, increased mortality and loss of confidence of community in the programme.[4]Another situation necessitating consideration here is HIV-TB co-infection. As the degree of immunosuppression worsens in these patients, cases with paucibacillary sputum samples begin to increase, who also have atypical findings on chest X-ray.[5] Reducing number of sputum samples for screening of tuberculosis in such patients will delay the diagnosis, miss the potential cases and their treatment. Thus, the suitability of this recommendation needs to be evaluated before applying it in HIV-TB co-infected population.

WHO has strongly recommended daily therapy in both HIV positive as well as negative population as opposed to conventional thrice weekly regimen. It may be a good suggestion in HIV positive patients,

Table 1: Summary of comments on individual recommendations

RECOMMENDATIONS	COMMENTS
RECOMMENDATIONS SUPPORTED	
A)**Recommendations for diagnosis**	
1) Discontinuation of use of categories to classify patients	Helps to improve priority status of MDR-TB
2) Discontinuation of using course of antibiotics to help in diagnosis of TB in HIV/AIDS patients.	Strongly supported; This recommendation will prevent delay in diagnosis and treatment initiation.
3) Use of 2 sputum samples instead of conventional 3 samples to screen for TB suspects	Applicable to settings with well functioning EQA as well as good internal quality control; significant limitation in resource constrained settings, where ensuring quality control may not be possible; caution in HIV- TB patients where higher number of paucibacillary cases
B)**Recommendations for treatment and follow-up**	
1) Treatment with SCC using 6 months of rifampicin	Already followed in national programmes in high burden countries (e.g. RNTCP in India);sufficient evidence to show unequivocal efficacy
2) Referral of end-IP sputum smear positive patients for DST	Useful in present circumstances but may not be operationally feasible everywhere, as many countries still lack desired infrastructure and resources to carry out DST on routine basis
3) Carrying out DST for previously-treated patients, and using rapid DST results to guide treatment regimen	
RECOMMENDATIONS REQUIRING MORE EVIDENCE	
1) Daily therapy in HIV-TB co-infected patients	Good suggestion, but paucity of sufficient evidence; trials with large sample size required to document clear cut benefits
2) Addition of ethambutol in continuation phase	Level of isoniazid resistance where this needs to be applied remains unknown; Increased risk of ocular toxicity (dose and duration dependent)[10]; Increased pill burden; Increased risk of acquired ethambutol resistance-deleterious for management of MDR-TB regimen
RECOMMENDATIONS NOT ACCEPTABLE	
1) Daily therapy in non- HIV patients	Success of DOTS establishes efficacy of intermittent regimen, high cure rates in India and China using intermittent therapy (85% and 90% respectively),[7]; Operational limitations of daily treatment; Lower incidence of certain important side-effects with intermittent treatment (hepatotoxicity, arthralgia)
2) Abandoning extension of IP phase in end-IP sputum positive patients	Study from Bangladesh reveals low relapse rates with IP-extension; No strong evidence showing benefit of discontinuation of IP extension
3) Isoniazid prophylaxis in household contacts and people living with HIV/AIDS who do not have active TB (irrespective of their HIV status)	Not suitable in country like India due to high reinfection rates and increasing INH resistance[11], with better ART services and lowering of threshold for initiating treatment, patient may not develop TB at all; lack of resources in developing countries
4) Empirical treatment for MDR-TB in patients with treatment failure/patients with high likelihood of MDR-TB	Chance of subjectivity in treatment decision; increased cost of treatment; limited capacity in high burden countries to treat MDR-TB
5) Inclusion of high dose INH for treatment of MDR-TB under programmatic setup	Requirement for facility to detect level of INH resistance, inadequate data on safety profile

SCC: Short Course Chemotherapy;DST: Drug Susceptibility Testing

where small clinical trials and studies have consistently shown better cure rates, lower frequencies of relapse and treatment failure with daily treatment.[6] Nevertheless, there is paucity of well-designed and adequately powered randomized trials, sufficiently addressing this problem in HIV-TB co-infection. The extension of this guideline to include HIV negative population should not have a blanket approach. All over the world, Directly Observed Treatment Short-Course (DOTS) strategy has already shown dramatic improvement in cure rates, establishing the efficacy of intermittent therapy. Data from India and China, two high burden countries with maximum number of tuberculosis patients have shown success rate* of treatment to be more than 85 % and 90% respectively with intermittent therapy.[7] Also, WHO report 2010 has shown that globally, the rate of treatment success for new sputum smear-positive cases of pulmonary TB, who were treated in the 2008 cohort was 86%, with improving trends.[7] No further evidence is required to prove effectiveness, tolerability and feasibility of intermittent regimen under a programmatic set up. In addition, numerous other reasons favour thrice weekly treatment. First, certain adverse effects (e.g. hepatotoxicity, arthralgia), are lower in alternate day regimen.[8,9] This is significant in Revised National Tuberculosis Control Programme's (RNTCP) decentralized treatment, where not every patient is under expert medical care. Second, beneficial results for daily therapy may not get converted into actual benefits in a programme, where individual treatment provider may choose to opt out due to increased work load. Third, high dropout rate is expected with daily treatment in countries like India, where patients have to travel long distances in villages to procure single dose of ATT. Considering these factors, it can be said that advantages of daily therapy may not be worth its risk. Therefore, further evidence is needed to document its clear cut benefit, and till that time, thrice weekly regimen remains 'acceptable' in a programmatic set up.

The guidelines also recommend addition of ethambutol in continuation phase in areas of high level of isoniazid resistance. This is a good suggestion; nonetheless, many obstacles need to be cleared before its implementation. First, the threshold of community INH resistance where this policy should be considered remains unknown. Second, though ethambutol is relatively free of side-effects, yet adding it in continuation phase would definitely increase risk of irreversible ocular side-effect.[10] As shown by observational studies, this is a duration dependent side effect and thus incidence is expected to increase many folds after its inclusion in Continuation Phase (CP).[10] Third, as mentioned in guidelines itself, there is inadequate evidence about ability of ethambutol to "protect rifampicin" in patients with pre-treatment isoniazid resistance. Fourth, addition of ethambutol implies increasing pill burden, which may be unnecessary in 82-85% of cases (in India, where the INH resistant rate is approx. 15-18%).[11,12] Last but not the least, chances of acquired resistance to ethambutol will increase after its inclusion for longer duration of treatment, adversely affecting treatment options for MDR-TB. Therefore, despite moderate INH resistance prevalent in India, the risk- benefit of adding ethambutol should be weighed before implementing this recommendation.[11, 12]

A short course of antibiotics is no longer recommended to aid in diagnosis of tuberculosis in sputum smear negative HIV-TB co-infected patients. This approach will help to reduce delay in treatment initiation, consequently decreasing morbidity and unnecessary cost of antibiotics. Thus, this recommendation is strongly supported and should be executed without hesitation.

Extra-pulmonary tuberculosis (EPTB) in patients with HIV/AIDS should have received greater emphasis. EPTB has higher incidence in retrovirus positive patients and usually portends poor prognosis. Diagnosis is usually based on the imaging studies due to difficulties in obtaining tissue diagnosis. This constitutes a significant limitation in developing countries, where such facilities may not be available.

* The success rate of treatment includes the percentage of new smear-positive patients who are cured (i.e., whose sputum smear is negative) plus the percentage who complete treatment without bacteriologic confirmation of cure

This, coupled with hazards of radiation exposure and need to undergo these investigations repeatedly for follow-up, makes them unsuitable for use in a programme. Another grey area in management of HIV-TB co-infection is the duration of treatment for both pulmonary as well as extra-pulmonary cases. Some authorities recommend extended duration of treatment whereas others do not. The reasons cited for not advocating extended duration of treatment are operational difficulties, stigmatisation of patients by separate regimen, drug interaction of rifampicin and a greater chance of acquired rifampicin resistance. However, one has to keep in mind the fact that HIV-TB co-infected patients are significantly more prone to relapse with higher case fatality rates.[13-15] Studies with longer duration of treatment (~8 months) have shown relapse rate to be much lower.[13]There is a need for guidelines to address these issues of diagnostic uncertainties in EPTB and conflicts regarding duration of treatment, documentation of cure and outcome in HIV-TB co-infection.

The guidelines further recommend discontinuation of extension of intensive phase (IP) for patients having positive sputum smear at the end of second month of treatment. No concrete evidence has been provided in support of this statement. Guidelines have mentioned one study, currently underway in Bangladesh, where preliminary results have revealed significantly lower relapse rate in patients with extension arm. Any increase in relapse rate will be deleterious in countries like India, where relapse notification rate is quite low. Besides, extending intensive phase promotes adherence to sputum monitoring, which is of great importance in identifying MDR suspects. End-IP extension is operationally feasible and there is no significant cost benefit achieved by its discontinuation. Hence, it should be continued without interruption.

Empirical treatment for MDR-TB in patients with treatment failure and other sub-groups with high likelihood of MDR-TB has been advocated by the current guideline. This recommendation has potential to introduce subjectivities in treatment decisions, unnecessarily exposing some patients to higher pill burden, undesirable side-effects of second-line drugs and *inconvenience* of taking injectables on daily basis. Moreover, it may lead to indiscriminatory use of second-line drugs, further contributing to the cost of therapy and drug resistance.

High dose isoniazid (INH) has been included as one of the options for treatment of MDR-TB. One requires facility to detect level of INH resistance before using this drug in higher doses. This is difficult in a programmatic setup, where number of samples becomes considerably large. Besides, safety profile of high dose isoniazid has not been studied adequately. These factors, along with limited resources in the high burden countries, make it a poor choice for treatment of MDR TB. Hence, use of high dose INH should be reconsidered in a programmatic set up and may be practised only as part of individualised therapy.

Isoniazid prophylaxis has been advocated in household contacts and people living with HIV/AIDS, who do not have active TB (irrespective of their HIV status). This is not suitable for application in countries like India, where chances of reinfection are high, nullifying any advantages gained by prophylaxis. Increasing isoniazid resistance will further decrease its effectiveness. More importantly, now more and more patients with HIV are initiated treatment at higher CD4 counts (less than 350 cells/µl), which decreases the probability of developing active tuberculosis. In resource constraint developing countries, the first priority should always be treatment of active disease with regular drug supply and quality medications.

Overall, the fourth edition has dealt with various problems of tuberculosis including drug resistance effectively. However, certain areas lack adequate evidence to implement the recommendations

as desired. There is immense requirement for clinical trials with good study design and large sample size to generate more evidence in order to rationalize treatment in all controversial areas. It is hoped that for the next edition, there will be wider representation from high burden countries, data based on sound evidence and recommendations to take care of existing conflicts in TB management. This will help to reduce mortality, morbidity and economic losses due to this disease, thereby improving TB scenario all over the world.

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