GUIDELINES FOR THE TREATMENT OF DRUG RESISTANT TUBERCULOSIS: THE 2018 REVISION

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Tuberculosis has been known to humans since time immemorial. The earliest recorded cases of tuberculosis originate from India and China, dating as far back as 3300 years and 2300 years respectively. It is known by many names, and is still a deadly disease affecting significant number of people worldwide. According to most recent estimates, tuberculosis was diagnosed in 10 million people worldwide in 2017, and deaths attributable to tuberculosis in year 2017 among HIV-negative individuals were 1.3 million. Tuberculosis caused additional 0.3 million deaths among people living with HIV. Two-thirds of cases of tuberculosis in year 2017 were from eight countries and Pakistan contributed 5% of the global burden of tuberculosis in the year 2017. According to the World Health Organization (WHO), Pakistan is among the top 20 countries which collectively contributed 84% and 87% to the world-wide burden of drug-susceptible and drug-resistant tuberculosis respectively in year 2017. Infact, Pakistan contributes 61% of the cases of tuberculosis in the eastern Mediterranean region and has been estimated to have 4\(^{th}\) highest burden of multi-drug resistant tuberculosis (MDR-TB) worldwide.

As with most of infectious diseases, drug resistant tuberculosis has become a common clinical entity that is very difficult to treat. In the year 2017, 0.55 million new cases of rifampicin resistant tuberculosis were detected worldwide, of which more than 80% were categorized as MDR-TB. Drug resistant tuberculosis (DRTB) stems from a number of causes, however, poor compliance with the treatment regimen is the most important and preventable cause of DRTB. In the incidence of DRTB in patients treated for tuberculosis is much higher than those not treated for tuberculosis as indicated by the incidence of DRTB in previously treated patients (18% vs 3.5%). This situation warrants improved efforts in urgent / timely diagnosis and treatment of DRTB as the global incidence of DRTB each year is increasing. With a treatment success rate of a little more than 50% for DRTB, efforts need to be aimed at prevention as well as treatment of DRTB to achieve a proposed 75% success rate for DRTB which was to be achieved by the end of 2015.

The WHO has been leading the efforts aimed at diagnosis and treatment of tuberculosis worldwide. It has been issuing guidelines for the treatment of both drug-susceptible and drug-resistant tuberculosis. Recently, the WHO issued a rapid communication on the treatment of drug resistant tuberculosis. It heralded a new era in the management of drug resistant tuberculosis by taking the injectable drugs out of the equation. According to the announcement, the medicines for use in the long-term regimen for the treatment of multi-drug resistant TB (MDR-TB) have been regrouped into three groups. The first group of Group A consists of fluoroquinolones, bedaquilline and linezolid. The second group or Group B consists of clofazimine and cycloserine or terizodone (either of the two) and the last group or Group C consists of ethambutol, delamanid, pyrazinamide, meropenem or imipenem-cilastatin (either of the two), amikacin or streptomycin (either of the two), ethionamide or protionamide (either of the two) and p-aminosalicylic acid. This regrouping is significant because the injectable agents, such as amikacin, capreomycin, kanamycin and streptomycin, which were previously considered first line agents for the treatment of DRTB, are no longer recommended as the first line agents. Aminoglycosides had been an integral part of the DRTB treatment regimen till now. They were considered first line agents and their inclusion in a regimen was considered to be necessary for the efficacy of the regimen in terms of DRTB cure.

Before the current announcement, injectables were usually recommended for at least 8 months in MDR TB and 12 months in XDR-TB. Their use has been associated with considerable toxicity and their use for the treatment of MDR-TB has been questioned. The injectables have to be administered via parenteral routes and this mode of administration is painful and causes distress to the patients in addition to causing a number of significant side effects including but not limited to permanent hearing loss. While aminoglycoside-induced hearing loss may rarely develop even after a single dose, it is more common in the settings of anti-tuberculosis treatment because they are administered for prolonged period, i.e., months, and because cumulative dose of aminoglycosides has been found to be predictive of hearing loss.

It is heartening to see that the dangers associated with the use of aminoglycosides have at last been realized and they have been taken off the drug regimen. But it is important to note that this decision has only been made possible in the light of success reported with newer agents such as linezolid, bedaquilline and delamanid as well as clofazimine, allowing for a choice of agents and re-structuring of DRTB treatment regimens. Additionally, newer anti TB agents such as...
sutezolid and pretomanid are being studied as potential members of future DRTB treatment regimens with hopefully shorter treatment duration, in some cases as short as 6 months.\textsuperscript{27–30}

While the detailed guidelines for management of drug resistant tuberculosis are yet to be published, the current recommendation looks good and a giant step towards simplifying the regimen.

This oral drug only regimen will most likely bolster treatment outcome by improving patient compliance and removing obstacles such as a need to access a health care giver for administration of injectables for prolonged periods of time. It is expected that the treatment duration of drug-resistant tuberculosis, particularly rifampicin resistant tuberculosis will be shortened by the approval and inclusion of newer agents. Although it is too early to say what the revised guidelines for the treatment of drug resistant tuberculosis by the WHO will suggest, it can now be said that the era of “better dead than dead” is finally over.

REFERENCES


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