Review Article

Multidrug-resistant and extensively drug-resistant tuberculosis (M/XDR-TB): management in special situations

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Abstract

Multidrug-resistant and extensively drug-resistant tuberculosis (M/XDR-TB) is an emerging field of interest that presents a lot of risk in the control of the disease worldwide, with having difficult and challenging issues regarding management. The prevalence of M/XDR-TB, in a community, mirrors the functional state and efficacy of tuberculosis control program and realistic attitude of the community toward implementation of such programs. The management of M/XDR-TB is difficult, much expensive, and even more challenging in special situations such as pregnancy, breastfeeding, contraception, children, diabetes mellitus, renal insufficiency, liver disorders, seizure disorders, psychiatric disorders, and substance dependence, and it quite often leads to treatment failure.

KEY WORDS: Multidrug-resistant tuberculosis, extensively drug-resistant tuberculosis, pregnancy, diabetes mellitus,

Introduction

Multidrug-resistant tuberculosis (MDR-TB) is defined as the disease owing to *Mycobacterium tuberculosis* that is resistant to isoniazid and rifampicin with or without resistance to other first-line anti-tubercular drugs provided the culture and drug susceptibility test (DST) result must be from a Revised National Tuberculosis Control Program (RNTCP) accredited laboratory. Extensively drug-resistant tuberculosis (XDR-TB) is defined as tuberculosis with resistance to at least isoniazid and rifampicin (MDR-TB) and further resistance to a fluoroquinolone and a second-line injectable agent (kanamycin, amikacin, or capreomycin). Programatic Management of Drug-resistant Tuberculosis (PMDT) formerly known as DOTS-PLUS is an integral component of RNTCP that manages MDR-TB patients under an implemented program infrastructure.[1] The strategy is designed to manage MDR-TB using the second-line anti-tubercular drugs within the directly observed treatment and short course chemotherapy (DOTS) strategy in developing countries such as India. It is observed that the occurrence of MDR-TB is brought down by DOTS largely than DOTS-PLUS in all the DOTS implementing units of the country; hence, DOTS-PLUS is required overtime. The RNTCP under PMDT recommends a standardized treatment regimen (STR) category four (CAT IV) regimen, comprising six drugs (kanamycin, levofloxacin, ethionamide, cycloserine, pyrazinamide, and ethambutol) during the 6–9 months of the intensive phase (IP) and four drugs (levofloxacin, ethionamide, cycloserine, and ethambutol) during the 18 months of the continuation phase (CP). Para-aminosalicylic acid (PAS) is included in the regimen as an alternative drug if any bactericidal drug (kanamycin, levofloxacin, pyrazinamide, and ethionamide) or any two bacteriostatic (ethambutol and cycloserine) drugs are not tolerated. This designed regimen is considerably appropriate for high TB prevalent nations and

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low to middle income countries such as India. The injectable agent should be administered for not less than 6 months, and the entire treatment period is minimum of 18 months beyond sputum conversion. A complete standardized second-line treatment has shown to be feasible and cost-effective in the treatment of MDR-TB. RNTCP has also recommended a standardized treatment for the management of XDR-TB patients under PMDT. Prospectively named "CATEGORY V," the regimen consists of seven drugs, with two reserve/substitute drugs. The Category V regimen consists of 24–30 months duration, with 6–12 months IP and 18 months CP. The IP consists of capreomycin, PAS, moxifloxacin, high-dose isoniazid (600–900 mg), clofazamine, linezolid, and amoxycillin/clavulanate, while the CP will consist of PAS, moxifloxacin, high-dose Isoniazid (600–900 mg), clofazamine, linezolid, and amoxycillin/clavulanate. Reserve/substitute drugs would be clarithromycin and thiacetazone. The shift from IP to CP will be done only after attaining culture conversion (i.e., two consecutive negative cultures taken at least 1 month apart. In case of delay in the culture conversion, the IP will be extended from 6 months up to a maximum of 12 months. When compared with drug sensitive tuberculosis, multidrug resistant and extensively drug resistant tuberculosis (M/XDR-TB) is more demanding in terms of cost and duration of treatment, higher adverse reactions to second-line drugs, resources required by the treatment providers, and the prolonged adherence required by the patients. To add to these issues, certain associated special situations make the treatment of M/XDR-TB more difficult.[2,3] This review article outlines the management of M/XDR-TB in special situations such as pregnancy, breastfeeding, contraception, children, diabetes mellitus, renal insufficiency, liver disorders, seizure disorders, psychiatric disorders, and substance dependence.

Management of M/XDR-TB in pregnancy

There is a lack of experience in treating pregnant women with M/XDR-TB. Although teratogenicity has been demonstrated in only a few of the drugs used to treat M/XDR-TB, all but ethambutol reveal uncertain safety information available. All this makes treating M/XDR-TB during pregnancy very challenging. It is prudent to solicit the opinion of an experienced gynecologist/obstetrician and chest physician while treating such patients.[4–8] Pregnancy test has to be conducted for all the female patients of childbearing age upon initial evaluation. Pregnancy is not a contraindication for the treatment of M/XDR-TB, which poses great risks to the lives of both the mother and fetus.[9,10] However, birth control is highly favored for all the nonpregnant women undergoing the therapy for M/XDR-TB because of the possible effects for both the mother and fetus resulting from frequent and severe adverse drug reactions. M/XDR-TB patients found to be pregnant before the treatment initiation or on treatment are evaluated taking into consideration the factors such as the risks and benefits of M/XDR-TB treatment, severity of the M/XDR-TB, gestational age, and potential risks to the fetus. The risks and benefits of the treatment should be carefully considered, with the primary goal of smear conversion to protect the health of both the mother and child, both before and after birth. As the majority of teratogenic effects develop in the first trimester, the therapy may be postponed until the second trimester. After an evaluation of the risks and benefits of the treatment, the choice to delay the initiation of the treatment should be agreed by both the patient and the doctor. The choice is based chiefly on clinical judgment achieved on the basis of severity of the disease. When the therapy is initiated, treatment is carried out with three or four oral second-line anti-TB drugs, which are possibly to be highly effective against the infecting strain plus pyrazinamide. The regimen should be strengthened with an injectable agent and other drugs that are required soon after postpartum.[6] For the most part, aminoglycosides have to be restricted in the regimens of pregnant patients as they can be, particularly, toxic to the developing fetal ear. Although capreomycin is found to possess the risk of ototoxicity, it is the injectable drug of choice if an injectable agent has to be utilized. The manifestation of the drug in the fetus is reduced by the choice of using capreomycin thrice weekly from the beginning. The risk of nausea and vomiting associated with pregnancy is elevated owing to ethionamide, and teratogenic effects have been noticed in animal studies. Probably, the use of ethionamide in pregnant patients must be nullified. The termination of pregnancy is considered if the mother's life is compromised. A medical abortion is suggested when the condition of the mother is very poor that a pregnancy would carry a significant risk to her life. A further management of M/XDR-TB patients who are pregnant before the initiation of M/XDR-TB treatment or while on M/XDR-TB treatment are based on the duration of pregnancy.[1] If, the The patients should be advised to opt for a medical termination of pregnancy (MTP) when the duration of pregnancy is < 20 weeks because of the probable grave risks to both the mother and fetus. The patient should be referred to a gynecologist/obstetrician for MTP if they agreed, following which M/XDR-TB treatment can be initiated if the patient has not started M/XDR-TB treatment or continued if the patient is already on M/XDR-TB treatment. For the patients who are unwilling for MTP or revealed a pregnancy of >20 weeks, the risk to both the mother and fetus need to be explained clearly, and a modified treatment for M/XDR-TB should be initiated. For the patients who are in the first trimester (≤ 12 weeks), kanamycin and ethionamide are omitted from the M/XDR-TB regimen and PAS added. Kanamycin is replaced with PAS for the patients whose first trimester is over. Postpartum, PAS may be replaced with kanamycin and prolonged until the completion of the IP. Pregnant M/XDR-TB patients need to be monitored carefully both in relation to the treatment and the progress of the pregnancy. This approach should yield good results, because the patient should be smear negative at the time of parturition, and the separation of the mother and infant is not required. Breastfeeding should be encouraged until the patient is sputum negative. Despite limited data on the safety and long-term use of fluoroquinolones, cycloserine, PAS, and

amoxicillin/clavulanate in pregnancy, they are considered the drug of choice for M/XDR-TB treatment during pregnancy. In order to create a more complete treatment, the injectable agents such as ethionamide/protionamide or other drugs that were withheld because of the pregnancy can be added back postpartum. The shift between IP and CP may not be clear, and the administration of the injectable agent can be followed for 3–6 months postpartum even in the middle of treatment. The total treatment duration is the same as for M/XDR-TB treatment. The child should receive Bacillus Calmette–Guérin (BCG) vaccination at birth as per WHO policy. As there is limited data on the safety of delamanid and bedaquiline in pregnancy for the treatment of M/XDR-TB, these drugs should be avoided.

Management of M/XDR-TB in breastfeeding

The best method to avoid the spread of the tubercle bacilli to the baby is to provide chemotherapy in a proper manner at the right time. A complete course of anti-TB treatment has to be undergone by a nursing woman with drug-resistant TB. While treating lactating mothers, most anti-TB drugs will be present in the breast milk in concentrations that would amount to only a meager fraction of the therapeutic dose used in an infant. However, any effect on infants of such exposure during the full course of M/XDR-TB treatment has not been established. Therefore, when resources are available, it is recommended to provide infant formula options as an alternative to breastfeeding, but evidence supporting this fact is weak. The mother and her baby should not be completely separated. However, if the mother is sputum smear-positive, the care of the infant should be left to the family members until she becomes sputum smear-negative, if this is feasible. The common time when the mother and infant are together should be spent in well-ventilated areas or outdoors. In some setups, the option of using a surgical mask or an N-95 respirator is given to the mother for barrier protection until she becomes sputum smear-negative. The recommended policies are different across the world regarding separation of the child from the mother and the use of top milk.[11] Apart from providing nutrition, the human milk possesses immunological benefits, and all efforts to continue breastfeeding in newborns with mothers presenting TB should be made. Expressed breast milk feeding can be used as a substitute, with personal hygiene when there are mothers with MDR-TB or smear-positive during delivery. Continued feeding with expressed milk in mothers with pulmonary TB who are contagious, untreated or treated (< 3 weeks) and proven MDR along with isolation has been suggested by the American Academy of Pediatrics (AAP).[12] The WHO recommends feeding under all circumstances, however, a close contact with the baby should be brought down.[13,14] DOTS recommend to encourage feeding when mother is smear-negative and isolation required if revealing MDR-TB.[1]

Management of M/XDR-TB in contraception

All women of child-bearing age who are receiving M/XDR-TB therapy should be advised to use birth-control measures because of the potential risk to both the mother and fetus. Any contraindication has not been found to the use of oral contraceptives with the nonrifamycin containing regimens. The idea that oral contraceptives might have decreased efficacy owing to vomiting and drug interactions with second-line drugs has to be evoked. Advise has to be given to these patients to take their contraceptives apart from times when they may experience vomiting caused by the anti-TB treatment. Patients, who vomit at any time directly after or within the first 2 h after, taking the contraceptive tablet, should use a barrier method of contraception until a full month of the contraceptive tablets can be tolerated. In a similar manner, all the women of child bearing age identified as DR-TB suspects should be advised to follow a consistent and correct contraceptive method until the results of culture and drug susceptibility test (DST) are available. In the case of patients with mono- and poly-resistant TB showing susceptibility rifampicin, the use of rifampicin interacts with the contraceptive drugs leading to a reduced efficacy of protection against pregnancy. The two options that a woman under oral contraception while getting rifampicin treatment can choose are following consultation with a physician, use of an oral contraceptive pill containing a higher dose of estrogen (50 μg); or use of another form of contraception. For patients who do not want to take additional pills and/or when protection against sexually transmitted diseases is also needed, condoms are found to be a considerable solution. Medroxyprogesterone intramuscular injections and other methods of contraception can also be considered.

Management of M/XDR-TB in children

The experience in the use of second-line drugs for extended periods in children has been reported to be less. A discussion with family members is important, particularly, at the beginning of the therapy. While creating a regimen, a careful analysis on the risks and benefits of each drug should be carried out. Children with drug-resistant TB generally exhibit primary resistance transmitted from an index case with drug-resistant TB. The DST when available should be used to guide therapy, although children with paucibacillary TB are often culture-negative. However, the drug-resistant TB must be confirmed by every single task bacteriologically by the use of DST and avoid exposing children unnecessarily to toxic drugs. It is only based on the results of DST and the history of the children exposure to anti-TB drugs that the treatment of culture-negative children with clinical evidence of active TB disease and contact with a documented case of drug-resistant TB is driven.[15] M/XDR-TB is a life-threatening condition and there is no contraindication of anti-TB drugs in children.

Safety data on children are not available on the new anti-TB drugs brought in to the market lately and should be considered for use in any extreme life-threatening cases, with risk/benefits fully revealed and intensive safety monitoring. The second-line drugs were accepted by the children who have undergone treatment for drug-resistant TB.[15,16] Although a reduced cartilage development in beagles puppies have been observed owing to the effect of fluoroquinolones,[17] experience in humans has not presented similar effects.[18,19] It is considered that the advantage of fluoroquinolones in treating M/XDR-TB in children outrank any risk. In addition, the use of ethionamide, PAS, and cycloserine in children is found to be effective and well tolerated. In general, the dose of anti-TB drugs should be according to body weight. Hence, the body weight of children is monitored, especially in the pediatric cases, with alterations in the doses as the weight of the child increases.[20] The doses of all drugs, including the fluoroquinolones, should be given at the higher end of the recommended ranges whenever possible, except ethambutol.[15–21] Ethambutol should be dosed at 15–25 mg/kg as similar in adults with M/XDR-TB because of weak evidence regarding safe dose of the drug in order to avoid optic neuritis.[22] However, it should be administered cautiously, as it is more difficult to monitor for optic neuritis in children when compared with adults. Assessment on the failure of treatment in children who are not culture-positive initially is found to be challenging. When a chest radiograph reveals constant abnormalities, it is not certain that it indicates a lack of improvement. In children, the loss of weight or, in general, lack of sufficient weight gain, is significant and frequently one of the initial signs of failure in the treatment. Hence, the weight of the children is always observed. It has been alleged that adolescents are at high risk of showing poor treatment effects through unreliable evidences. The treatment effects in this group can be enhanced through early diagnosis, strong social support, individual and family counseling, and a close relationship with the medical provider.[23] The slow and tedious conventional solid phenotypic culture and DST methods although considered to be gold standard for diagnosis of MDR-TB but have been recently replaced by quicker methods. The WHO has accredited light emitting diode (LED) flourescence microscopy and liquid-based mycobacteria growth indicator tube (MGIT) for rapid results, as the recovery of tubercle bacilli is higher, the time to detection is shorter than with solid culture methods, and the test sensitivity is increased allowing the screening of a larger number of slides at the peripheral level without increasing overall costs.[14,24] The disadvantage is that liquid culture media, being a more sensitive culture system, presents higher contamination rates than solid media. Indirect methods that include rapid interferon gamma assays and T-SPOT using antigens ESAT-6, CFP-10, and TB7 have shown inconsistent results in children.[25] The WHO endorsed the Xpert MTB/RIF assay, a cartridge-based fully automated molecular diagnostic assay that uses real-time PCR to identify *M. tuberculosis* complex DNA and the mutations associated with rifampicin resistance directly from sputum specimens, in less than 2 h.[26] The assay has similar sensitivity, specificity, and accuracy as the culture on solid media. According to the WHO, it has been suggested that Xpert MTB/RIF should be preferred in comparison with the usual procedures followed such as the conventional microscopy, culture, and DST for the initial diagnosis of children suspected with MDR-TB or HIV-associated TB.[14] Large trials using Xpert MTB/RIF in children have been useful for rapid diagnosis in communities with a high burden of MDR-TB.[27] Molecular LPAs enable a quick detection of resistance to rifampicin individually or in combination with isoniazid. The line probe assays (LPAs) are lately suitable for use with AFB smear-positive sputum specimens or on *M. tuberculosis* isolates grown by the usual culture methods. Current evidence states that molecular LPAs such as Geno Type MTBDR plus assay and the Inno-LiPA Rif TB assay are costly and found to be of great utility in adults when compared with children.[28,29] Molecular LPAs and the Xpert MTB/RIF are presently the only two molecular technologies endorsed by the WHO for the genotypic detection of rifampicin resistance.[14] The advantages of detection of rifampicin resistance rapidly aids in prompt screening of patients at risk of MDR-TB and allows for early interruption of MDR-TB transmission. Despite benefits, the use of molecular tests does not eliminate the need for conventional culture and DST capability. Culture is primarily required for monitoring MDR-TB patient's response to therapy and for performing second-line DST.[14]

Management OF M/XDR-TB IN diabetes mellitus

The management of diabetes must be carried out closely throughout the treatment of M/XDR-TB. The health-care provider should be in touch with the physician who manages the patient's diabetes. Diabetic patients with M/XDR-TB are at risk for poor outcomes. In addition, the presence of diabetes mellitus may potentiate the severe effects of anti-TB drugs, especially renal dysfunction and peripheral neuropathy. Oral hypoglycemic agents are not contraindicated during the treatment of M/XDR-TB but may require an increase in the dosage. The use of ethionamide or protionamide may make it very challenging to control insulin levels. The creatinine and potassium levels should be checked very often, to a certain extent weekly for the first month and, then, at least monthly thereafter.[14]

Management of M/XDR-TB in renal insufficiency

Renal insufficiency owing to long standing TB disease itself, previous use of aminoglycosides or concurrent renal disease, is common. Great care should be taken in the While administering the second-line drugs in patients with renal impairment, proper care has to be provided. The dosing is based on

the patient's creatinine clearance, which is an estimate of the glomerular filtration rate. Creatinine clearance is calculated by the formula Weight (kg) × (140 – age) × (constant)/serum creatinine (μmol/L) (constant in the formula is = 1.23 for men and 1.04 for women). Consideration needs to be taken that M/XDR-TB patients require aminoglycosides for 6 months or more. The other drugs such as ethambutol, quinolones, cycloserine, and PAS may need dose or interval adjustment in the presence of mild to moderate renal impairment. In the presence of severe renal impairment many other drugs may also require adjustments as given in Table 1. In patients with M/XDR-TB, blood urea and serum creatinine should be monitored before the treatment initiation, monthly for 3 months after treatment initiation and then every three months while injection kanamycin is being administered. In patients with mild renal impairment, the dose of aminoglycosides may be reduced. In the presence of severe renal failure, the aminoglycoside therapy should be stopped and replaced with other potent nonnephrotoxic anti-TB drugs.[30]

Management of M/XDR-TB in liver disorders

Pyrazinamide is the most hepatotoxic of the three first-line drugs (rifampicin, isoniazid, and pyrazinamide). The second-line drugs such as ethionamide, protionamide, and PAS can also be hepatotoxic but less so than any of the first-line drugs. The prevalence of hepatitis is found to be uncommon with the fluoroquinolones. The potential for hepatotoxicity is elevated in elderly persons, those who consume alcohol, and those with pre-existing liver disease. The majority of the second-line drugs can be safely used in the presence of mild hepatic impairment, because they are relatively less hepatotoxic than the first-line drugs. However, pyrazinamide should be not be used in such patients. A careful monitoring of the liver enzymes is required even though other drugs can be used. The use of drugs may be withdrawn if they are found to intensify the inflammation of the liver. When a patient on second-line drugs develops hepatitis, other etiologies should also be excluded such as viral hepatitis, alcoholic hepatitis and drug-induced hepatitis by nonTB drugs.[31] It is unusual for a patient with TB to present concurrent acute hepatitis that is unrelated to TB or anti-TB treatment; here, clinical judgment is required. In a few cases, the anti-TB treatment can be deferred until the acute hepatitis has been resolved. The combination of four nonhepatotoxic drugs is the safest option in other cases for treating drug-resistant TB during acute hepatitis. The treatment for viral hepatitis can be carried out after a clinical diagnosis, and the treatment can be done during drug-resistant TB treatment.

Management of M/XDR-TB in seizure disorders

TB might itself involve the central nervous system and may cause seizures. However, the occurrence of seizures for the first time during anti-TB therapy is probably owing to the adverse effects generated by any of the anti-TB drugs. The second-line drugs such as cycloserine, ethionamide, and fluoroquinolones have been associated with seizures. A significant risk of seizure can be caused by high-dose isoniazid and, hence, it should be avoided in patients with active seizure disorders. Some patients who require treatment for M/XDR-TB may reveal presently or a history of the existence of a seizure disorder. In order to analyze such patients, the initial step is to determine whether the seizure disorder is under control and whether the patient is taking anti-seizure medication to control the same. An initiation or adjustment of anti-seizure medications will be required before beginning the M/XDR-TB therapy, if no control over the seizures is observed. Moreover, other underlying conditions or causes for seizures, if present, should be corrected. Pyridoxine should be administered along with cycloserine to inhibit seizures. The suggested prophylactic dose for at-risk patients on isoniazid is 10 to 25 mg/day and for patients on cycloserine is 25 mg of pyridoxine for every 250 mg of cycloserine daily. Cycloserine should, however, not be used in patients with active seizure disorders that are not well controlled with medication. In cases where no other drug is appropriate, cycloserine can be given and the anti-seizure medication adjusted as needed to control the seizure disorder. The risks and benefits about the use of cycloserine should be discussed with the patient, and the decision regarding the use of cycloserine is made together with the patient. Anti-epileptic drugs such as phenytoin increases metabolism of cycloserine and quinolones leading to low serum concentration. Therefore, high doses of cycloserine and quinolones may be required in patients with seizure disorder on anti-epileptic medications. Hence, close monitoring of serum levels of anti-epileptic drugs should be done preferably, if facility exists.[31,32]

Management of M/XDR-TB in substance dependence

Patients with substance-dependence disorders should be provided treatment for addiction. Complete denial from alcohol or other substances should be firmly stimulated, although active consumption is not a contraindication for anti-tuberculosis (anti-TB) treatment. The treatment might get affected on account of the patient's dependence; if this occurs repeatedly, the therapy should be suspended until successful treatment or measures to ensure adherence have been completed. Good directly observed therapy (DOT) gives the patient contact with and support from health-care providers, which often allows complete treatment even in patients with substance dependence. Patients dependent on alcohol or other substances will experience the increased occurrence of adverse effects of cycloserine including higher incidence of seizures. However, cycloserine should be used if required for the therapy, and the patient is closely monitored for the severe effects that are then adequately treated.

Table 1: Dosing recommendation for the adult patients with renal insufficiency or undergoing hemodialysis

Drug	Change in frequency	Dose and frequency in patients with creatinine clearance < 30 mL/min or those on hemodialysis
Pyrazinamide	Yes	25–35 mg/kg per dose three times a week
Ethambutol	Yes	15–25 mg/kg per dose three times a week
Levofloxacin	Yes	750–1,000 mg per dose three times a week
Ofloxacin	Yes	600–800 mg per dose three times per week (not daily)
Moxifloxacin	No change	400 mg once daily
Cycloserine	Yes	250 mg daily or 500 mg three times a week
Terizidone	—	Recommendations not available
Ethionamide/prothionamide	No change needed	250–500 mg daily
Para-aminosalicylic acid	No change needed	4 g/dose twice daily
Capreomycin	Yes	12–15 mg/kg/dose twice or three times a week
Kanamycin	Yes	12–15 mg/kg/dose twice or three times a week
Amikacin	Yes	12–15 mg/kg/dose twice or three times a week
Clarithromycin	Yes	Usual dose 500 mg twice daily but can be reduced to 250 mg twice daily
Linezolid	No change needed*	Usual adult dose is 600 mg twice daily (can be reduced to 600 mg OD after 4–6 weeks)[a]
Clofazimine	Yes	Begin at 300 mg daily and decrease to 100 mg after 4–6 weeks
Amoxicillin and clavulanic acid	Yes	Dose used is 625 mg twice daily, 1,000 mg should not be administered
Rifabutin	No change needed	Normal dose can be used
Rifapentine	No change needed	
Meropenem	Yes	For creatinine clearance 20–40 mL/min dose 750 mg every 12 h; for creatinine clearance < 20 mL/min dose 500 mg every 12 h
Imipenem/cilastatin	Yes	For creatinine clearance 20–40 mL/min dose 500 mg every 8 h; for creatinine clearance < 20 mL/min dose 500 mg every12 h
High-dose isoniazid	—	Recommendations not available
Delamanid		Recommendations not available
Bedaquiline	-	No dosage adjustment is required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment) and use with caution

[a]The pharmacokinetics of the parent drug, linezolid, is not altered in patients with any degree of renal insufficiency; however, the two primary metabolites of linezolid may accumulate in patients with renal insufficiency, with the amount of accumulation increasing with the severity of renal dysfunction. The clinical significance of accumulation of these two metabolites has not been determined in patients with severe renal insufficiency. However, given the absence of information on the clinical significance of accumulation of the primary metabolites; use of linezolid in patients with renal insufficiency should be weighed against the potential risks of accumulation of these metabolites.

M/XDR-TB in patients with psychosis

There is an increased baseline incidence of depression and anxiety in patients with M/XDR-TB, often because of the chronic condition and socioeconomic stress factors related to the disease. For M/XDR-TB patients with a concurrent psychiatric illness, it is advisable to consult a a psychiatrist before the initiation of the treatment for M/XDR-TB. The initial evaluation documents of any pre-existing psychiatric condition establish a baseline for comparison, if new psychiatric symptoms develop while the patient is on treatment. Psychiatric illness, if any, at the beginning or during treatment should be completely attended. If a health-care worker with psychiatric training is not available, the treating health-care provider should document any psychiatric conditions the patient may exhibit at the initial evaluation. In order to manage the patient with a psychiatric condition or showing adverse psychiatric effects owing to medication, methods such as treatment with psychiatric medication, individual counseling, and/or group therapy may be required.[13,33,34] Fluoroquinolones and ethionamide are related to psychosis. Pyridoxine prophylaxis can bring down the risk of neurologic and psychiatric adverse reactions.

Cycloserine may cause severe psychosis and depression leading to suicidal tendencies. However, cycloserine utilization is not totally contraindicated for the psychiatric patient. In a psychiatric patient, the severe effects of cycloserine are very pronounced, but the benefits of using this drug often exceed the potential higher risk of adverse effects. If cycloserine is used in patients with psychiatric disorders, a close monitoring is suggested. When a patient on cycloserine therapy develops psychosis, anti-psychotic treatment should be initiated and cycloserine therapy should be temporarily withdrawn. After the symptoms resolve and the patient is stabilized, cycloserine therapy may be resumed. Such patients may require anti-psychotic treatment till anti-TB treatment is completed. When any patient on M/XDR-TB treatment develops psychosis, other etiologies such as psychosocial stresses, depression, hypothyroidism, illicit drug, and alcohol use should also be taken care of.

Conclusion

Management of M/XDR-TB is difficult, much expensive, and even more challenging in special situations such as pregnancy, breastfeeding, contraception, children, diabetes mellitus, renal insufficiency, liver disorders, seizure disorders, psychiatric disorders, and substance dependence and quite often leads to treatment failure.

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