Review Article

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Management of MDR-TB: Review of Iran's Experience

Mohammad Reza Masjedi [1], Payam Tabarsi [2,3], Majid Marjani [3], Parvaneh Baghaei Shiva [3], Mahshid Nasehi [4], Mohammad Mehdi Gooya [4], Parisa Farnia [2], and Ali Akbar Velayati [3]

[1] Chronic Respiratory Diseases Research Center, [2] Mycobacteriology Research Center, [3] Clinical Tuberculosis and Epidemiology Research Center, NRITLD, Shahid Beheshti University of Medical Science, [4] Center for Disease Control and Prevention, Ministry of Health and Medical Education, Tehran, Iran

Correspondence to: Tabarsi P
Address: NRITLD, Shaheed Bahonar Ave, Darabad, TEHRAN 19569, P.O:19575/154, IRAN
Email address:payamtabarsi@yahoo.com

INTRODUCTION

Emergence of drug resistance during the course of tuberculosis (TB) treatment and especially development of multi-drug resistant (MDR) TB is a major health hazard in many countries worldwide and is considered as an obstacle against TB control (1).

MDR-TB is caused by a Mycobacterium tuberculosis strain which is at least resistant to isoniazid and rifampin and usually occurs as the result of incomplete or inadequate treatment (2). Annually, about 425,000 new MDR-TB cases occur in the world which constitutes about 5% of overall global TB burden (2). Its prevalence worldwide is approximately 2 to 3 times this number (3). Diagnosis of MDR-TB requires an equipped laboratory which is not available in many parts of the world. Treatment of MDR-TB takes roughly 20 months; whereas, treatment of drug-susceptible TB takes 6-9 months (4). Furthermore, second line medications used for treatment of MDR-TB have greater side effects and are more costly. Treatment of MDR-TB is approximately 100 to 300 times more expensive than drug sensitive TB (5, 6). Also, treatment success rate for MDR-TB is lower and it is associated with higher rates of morbidity and mortality compared to drug sensitive TB (4).

Treatment success rate for meticulously designed MDR-TB treatment protocols with low prevalence of HIV is often in the range of 70-80% while this rate is about 90% for drug sensitive TB (7, 8). However, treatment of patients with MDR-TB is necessary to prevent its dissemination. About 70% of patients will recover with the current treatment protocol (8). Eastern Mediterranean Region constitutes 6% of overall global TB and approximately 4.3% of MDR-TB cases (2, 7). Incidence of MDR-TB in this region is 3.3% of all TB cases out of which, 50% or 9000 cases occur in Pakistan. The remaining 6 countries include Afghanistan, Sudan, Iran, Iraq, Morocco and Egypt each with more than 1000 MDR-TB cases annually (2).

The World Health Organization (WHO) estimates 1,305 cases of MDR-TB annually in Iran. Prevalence of MDR-TB is approximately 5% among new TB and 48.2% among retreatment TB cases (8); whereas, in 2006 only 28 cases of MDR-TB were detected which highlights the need for fast development of a national laboratory network for performing culture and drug susceptibility testing.

In which patients drug susceptibility testing (DST) has to be performed?

Ideally, drug susceptibility testing had better be performed for all pulmonary TB patients. However, in situations where necessary equipments are not available

for culture and DST of all patients, this test should be performed for individuals at high risk of drug resistance (4, 9) including the following groups:

1. Patients with treatment failure in the second treatment group and chronic TB cases (most high risk)
2. Individuals with close contact with diagnosed MDR-TB patients, if they have clinical symptoms suspicious of pulmonary TB
3. Patients with treatment failure in the first treatment group
4. Patients whose sputum smear at the end of the acute phase of treatment becomes or still remains positive
5. Cases with recurrence or default (although the possibility of drug resistance in them is lower compared to the aforementioned groups)
6. Patients with pulmonary TB / HIV
7. Imprisoned patients with smear positive pulmonary TB

Identification (determination of the Mycobacterium strain)

Considering the fact that non-tuberculous mycobacteria are resistant to first line anti-TB drugs (except for Mycobacterium kansasii), it is necessary to determine Mycobacterium strain before the initiation of anti-MDR-TB treatment. At present, about 10-12% of MDR-TB cases referred to medical centers for treatment are caused by non-tuberculous mycobacteria (4, 10).

TREATMENT

A. Classification of anti-TB drugs

Anti-TB medications used for treatment of MDR-TB are categorized into 5 major groups (10).

1. First line oral agents: These drugs are the most potent anti-TB medications and are well tolerated. For treatment of MDR-TB, these drugs are used only when drug susceptibility testing indicates susceptibility (4, 11).
2. Injectable anti-TB agents: These drugs should be administered for all patients with MDR-TB. Streptomycin is the first line drug in this group. However, due to the high rate of drug resistance to this drug among MDR-TB patients, it is usually not an appropriate choice. Amikacin and Kanamycin are good choices for these patients. These two drugs are very much alike and have 100% cross-resistance. If the microorganism is resistant to these drugs, capreomycin would be the next choice (4, 11).
3. Fluoroquinolones: This group is also among the main medications for treatment of MDR-TB. Effective quinolones on M. tuberculosis include moxifloxacin, gatifloxacin, levofloxacin and ofloxacin in order of efficacy (10, 12). At present, ciprofloxacin is not recommended for treatment of MDR-TB.
4. Oral bacteriostatic second-line agents: Drugs of this category are often used for treatment of MDR-TB. The main drugs in this group include para-aminosalicylic acid (PAS), ethionamide, prothionamide and cycloserine. In terms of efficacy, ethionamide and PAS are more efficacious but are usually not administered simultaneously because the risk of gastrointestinal complications and hypothyroidism will rise (4).
5. Miscellaneous drugs (agents with unclear role in treatment of MDR-TB): This group is not among the conventional MDR-TB drug regimen. However, they may be used in cases where the number of selected drugs does not reach the ideal required number (at least 4 efficient drugs).

Treatment regimen: In order for a regimen to be efficacious, 4 effective drugs should be included in that regimen. These drugs are selected based on drug susceptibility testing and history of drug intake by the patient (9, 13). In Iran, considering the limited availability of second line agents and not having a routine access to drug susceptibility testing for the second line drugs, a standard regimen is used for treatment of MDR-TB patients which includes levofloxacin or ofloxacin + amikacin +cycloserine + prothionamide + ethambutol +pyrazinamide (8, 14).

Drug dosages are presented in Table 1.

Table 1. Anti-tuberculosis drug used in the treatment of MDR-TB and their dosages.

Drugs	Dosages
EMB	15-25 mg/kg/day
PZA	20-30 mg/kg/day
AMK	15 mg/kg/day(5 day/week. Maximum 1g/day)
Amoxicillin-Clavulanate	2-4 g daily
Clarithromycin	1000 mg/day
PTH	750-1000 mg/day
CS	750-1000 mg/day
OFX	400-800 mg/day
LVX	750-1000 mg/day

MDR-TB= multidrug-resistant tuberculosis; EMB=ethambutol; PZA= pyrazinamide; AMK=amikacin; PTH=prothinanmide; CS=cycloserin; OFX=ofloxacin: LVX=Levofloxacin

Important points:

1. Some anti-TB first line agents may be added to the standard above-mentioned regimen if proven susceptible in drug susceptibility testing (4)
2. If any of the drugs in the above-mentioned regimen cannot be administered for some reason, a fifth-group medication will be added to the regimen (4).
3. In cases where drug susceptibility testing indicates resistance to second line agents or if the patient has extensive bilateral pulmonary involvement, more than 4 drugs will be included in the regimen (4)(at present, co-amoxiclav and clarithromycin are the drugs that will be added to the regimen)
4. Treatment of extra-pulmonary MDR-TB is similar to that of pulmonary TB (15).
5. In all patients that use cycloserine, concomitant administration of vitamin B6 is necessary to prevent neural complications (4).

How long should the administration of injectable anti-TB agents continue?

Injectable anti-TB agents should at least continue for 8 months and preferably an additional 4 months after the sputum smear becomes negative (4, 11). For cases with insufficient number of effective medications in their drug regimen or those with extensive bilateral pulmonary involvement, treatment with amikacin may be extended for longer periods of time (4).

Duration of Treatment:

Treatment course should continue for 20 months and at least 18 months after the sputum smear becomes negative (4, 11).

Figure 1 summarizes the phases of treatment.

Surgical treatment:

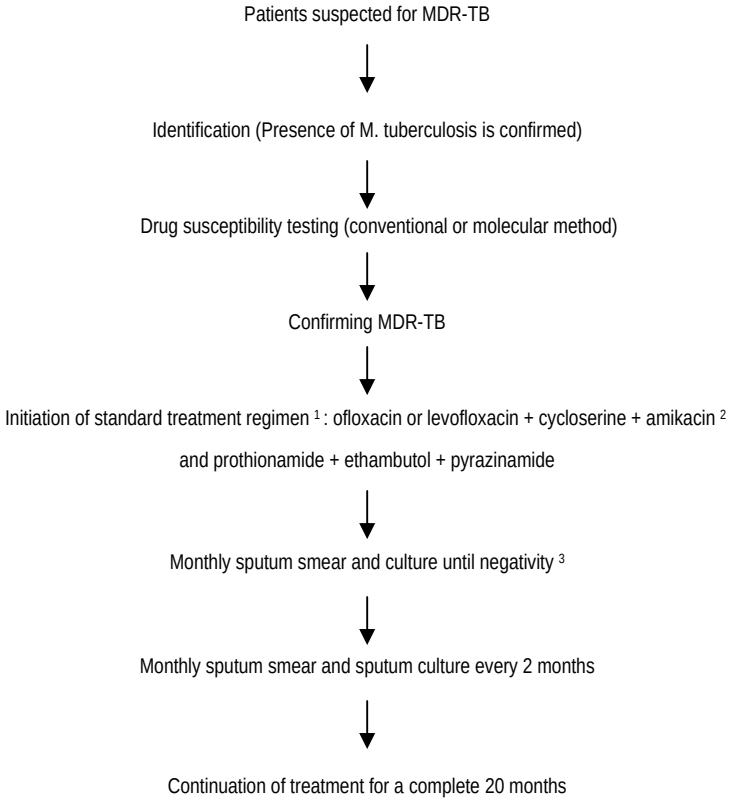
The most common surgical procedure in MDR-TB patients is partial or complete surgical resection of the lung. Surgical resection under special circumstances will be safe and effective. However, this procedure should be performed by a skillful thoracic surgeon and requires ideal post-operative care. Infection control protocols should be precisely followed as well. Surgical treatment is mostly recommended at the onset of disease when infection is confined to one lobe or one lung. Surgery is contraindicated when both lungs are extensively involved. The patient should be on anti-TB drug regimen for at least 2 months prior to surgery. Pharmaceutical treatment should also continue for 12-24 months post-operatively (4, 16, 17).

Treatment of MDR-TB in special circumstances

1. Pregnancy: All women have to take a pregnancy test before the initiation of MDR-TB treatment and contraception is strongly recommended during the course of MDR-TB treatment. If a pregnant woman contracts MDR-TB, treatment is recommended since active TB carries a high risk for both the mother and the fetus. If the symptoms are mild and the patient consents, treatment can be initiated in the second trimester. However, if clinical and radiographic signs and symptoms are severe, treatment has to be initiated right away regardless of how far along she is in her pregnancy. Among the second line agents, injectable aminoglycosides and ethionamide should be avoided as much as possible; although, there are some case studies regarding the safety of these drugs during pregnancy (4, 17).

2. Nursing: Since the majority of anti-TB medications reach a high concentration in the mother's milk, it is recommended for mothers under MDR-TB medication not to breast-feed their infants and use formula (4).
3. Children: Children under treatment for MDR-TB have mostly been in close contact with an MDR-TB patient because TB infection in children is usually associated with small number of bacilli and therefore, culture and drug susceptibility testing are usually not an option for such patients.

For children in close contact with an MDR-TB patient, drug regimen will be determined based on the results of drug susceptibility testing of the index patient. Studies on the administration of second line agents in children are scarce. However, considering the dangers of MDR-TB, prescription of five second line agents is not prohibited in children and it has been demonstrated that when second line agents have been used in children, these drugs have been well tolerated (4).



1: In case of susceptibility, ethambutol and pyrazinamide are also added to the regimen.

2: Amikacin needs to be continued for at least 8 months after its initiation (it had better be continued until at least 4 months after the negativity of sputum smear)

3: Sputum smear is considered negative in case of presence of two negative smears with at least a 30 day interval.

Figure 1. Algorithm of MDR-TB treatment

XDR TB: The new definition of XDR TB is resistance to isoniazid and rifampin in addition to a quinolone and an injectable drug (18)

At present, XDR TB has turned into a major health dilemma. Its treatment is extremely difficult and the associated morbidity and mortality in patients especially in susceptible individuals like the HIV positive patients is high (19).

Treatment of XDR-TB with the abovementioned standard regimen is not much successful and the treatment success rate in such patients is estimated at 40% (20, 21, 22). Thus, all these patients have to be referred to the National Referral Center before any therapeutic intervention.

Currently, the XDR-TB treatment regimen in Iran is as follows:

Levofloxacin + Capreomycin +PAS +Prothionamide + Co-amoxiclav + Clofazimine +Linezolid or Imipenem

In XDR-TB drug regimen, the injectable drug must be continued for at least 12 months and throughout the entire treatment course if possible.

Pretreatment assessment of patients

In addition to taking a history and performing a full clinical examination, the following conditions should be specifically asked from the patient: diabetes, renal insufficiency, acute or chronic liver disease, thyroid disease, mental illness, alcohol consumption or substance abuse, HIV and pregnancy (4).

Assessment of patients during the course of treatment:

The clinical symptoms usually disappear during the first months of treatment. Radiographic changes are mostly delayed. Thus, chest X-ray has to be repeated every 6 months unless the patient requires surgical intervention or patient's general status changes. The most important sign of recovery is the negativity of sputum smear and culture. Between these two, culture has a greater sensitivity and must be necessarily performed (4).

Sputum smear and culture should be repeated monthly until they become negative (twice with a 30 day interval). After negativity, sputum smear needs to be repeated monthly and sputum culture every two months (Tables 2-5).

Assessment of drug side effects during the treatment:

The common adverse effects and complications that usually occur during the course of MDR-TB treatment must be asked from the patient in every visit by the physician in charge of treatment of that patient. These adverse effects include rash, GI complications, signs and symptoms of psychosis, jaundice, hearing loss, peripheral neuropathy, palpitation and muscle cramp (4). Nephrotoxicity is a recognized complication of aminoglycosides which is usually not recognizable by taking a history. Serum creatinine level must be checked monthly. In patients with a history of renal disease, in the elderly and in those with any sign or symptom of renal disease more precise measurement of creatinine is essential.

Electrolyte excretion is a known side effect of injectable anti-TB medications especially capreomycin. This is often a late complication and is reversible by discontinuation of injectable drugs. Monthly measurement of serum potassium is recommended in these patients.

Hypothyroidism is a late complication of PAS and ethionamide. This complication is usually suspected based on the clinical symptoms and is confirmed by measuring TSH. Measurement of serum TSH is recommended every 6 months. If symptoms appear, replacement therapy with levothyroxine is indicated.

In order to prevent neurologic complications of cycloserine, administration of vitamin B6 is essential. The recommended dosage is 50 mg vitamin B6 for each 250 mg of cycloserine administered (4).

The incidence of various adverse effects of MDR-TB treatment is demonstrated in Table 2.

Table 2. Major and Minor adverse effects of drugs in MDR-TB patients.

Adverse effects	Number of Patients with such condition: n(%)	Mean Interval ±SD (days)
Major Effect		
Neurologic side effects	7(8.8)	76.38±89.87 (13-240)
Hepatitis	4(5.0)	19±18.38 (3-45)
Renal Toxicity	3(3.8)	14±1.00 (13-15)
Auditory Toxicity	8(10)	56.38±63.52 (3-190)
Minor Effect		
Tinnitus	4(5.0)	60.33±44.81 (32-112)
Vertigo	5(6.3)	43.50±47.40 (6-112)
Nausea	13(16.3)	17.25±14.17 (4-47)
Vomiting	10(12.5)	28.50±41.32 (4-112)
Abdominal pain	11(13.8)	34.11±31.77 (8-112)
Weakness	3(3.8)	8.50±10.61 (1-16)
Pruritus	6(7.5)	19.33±12.74 (3-42)
Headache	2(2.5)	22±4.24 (19-25)
Anorexia	2(2.5)	11±11.31 (3-19)
Arthralgia	5(6.3)	23.40±23.85 (3-47)
Fever	4(5.0)	18±15.45 (3-39)

Important points regarding the assessment of patients during treatment:

1. The patients have to be visited by the physician in charge of their MDR-TB treatment monthly at first until negativity and every 6 months after that.
2. DOTS must better be implemented for drug consumption by the patients during the course of treatment.
3. Sputum smear and culture must be done monthly until negativity and after that sputum smear must be done monthly and sputum culture every two months.
4. Patients must receive daily injections.
5. Chest X-ray must be obtained at first and then every 6 months. In patients requiring surgery or those with a worsening respiratory status, chest X-ray may be obtained at any time.
6. Serum creatinine level should be monitored at first and then monthly (until using amikacin). In high risk patients, HIV positives or diabetics it better be checked every 1-3 weeks.
7. Serum potassium concentration should be monitored monthly until using Amikacin. In HIV positives, diabetics or other high risk patients it should be measured every 1-3 weeks.
8. In case of using pyrazinamide, liver tests should be ordered every 1-3 months. In HIV positives monthly testing is recommend.
9. All patients have to be evaluated and tested for concomitant HIV infection.
10. In HIV positive patients that use zidovudine, CBC test should be performed monthly at first and then whenever indicated based on symptoms.
11. In patients that receive antiretroviral medications, if symptoms appear, evaluation for lactic acidosis is recommended (23, 24).

Management of adverse effects:

Many complications during the treatment course of MDR-TB are transient. The physician needs to talk to the patient and explain that the complication is not dangerous and will be resolved and there is no need to discontinue the drugs or reduce their dosage. Considering the fact that treatment of MDR-TB in our country is according to the standard protocol, discontinuation of drugs because of related complications makes the treatment regimen incomplete and will adversely affect the outcome. Thus, in case of appearance of drug-related adverse effects, it is necessary to consult with MDR-TB specialists regarding the continuation or discontinuation of drugs.

Table 3. Treatment of single-drug or multi-drug resistant TB cases

Type of resistance	Recommended regimen	Duration of treatment course	Explanation
H (±S)	R, Z, and E	6-9 months	In patients with extensive pulmonary involvement a quinolone is added
H and Z	R,E,Fluoroquinolone	9-12 months	An extended treatment course is recommended in patients with extensive involvement
H and E	R,Z, and Fluroquinolone	9-12 months	An extended treatment course is recommended in patients with extensive involvement
R	H,E, Fluroquinolone plus at least 2 Monthsof Z	12-18 months	An extended treatment course is recommended in patients with extensive involvement
R and E (±S)	H,Z, Fluoroguinoline, plusan injectable agent for at least the first 2-3 month	18 months	In patients with severe involvement injectable agents have to be administered for a longer period of time (6 months)
R and Z (±S)	H,E, Fluroquinolone plus an injectable agent for at least the first 2-3 months	18 months	In patients with severe involvement injectable agents have to be administered for a longer period of time (6 months)
H,E,Z (±S)	R, Fluroquinolone, plus and oral second line agent plus anijectable agemls 2-3 months	18 months	In patients with severe involvement injectable agents have to be administered for a longer period of time (6 months)

Table 4. Groups of drugs to treat MDR-TB [a]

Group	Drugs (abbreviations)
Group1: First-line oral agents	• Pyrazinamide (Z) • Ethambutol (E) • Rifabutin (Rfb)
Group 2: Injectable agents	• Kanamycin (Km) • Amikacin (Am) • Capreomycin (Cm)
Group 3: Fluroquinolones	• Levofloxacin (Lfx) • Moxifloxacin (Mfx) • Ofloxacin (Ofx)
Group 4: Oral bacteriostatic second-line	• Para-aminosalucyluc acid (PAS) • Cycloserine (Cs) • Terizidone (Trd) • Ethionamide (Eto) • Protionamide (Pto)
Group 5: Agents with unclear role in treatment of drug resitant-TB	• Clofazimine (Cfz) • Linezolid (Lzd) • Amoxicillin/clavulanate (Amx/Clv) • Thioacetazone (Thz) • Imipenem/cilastatin (Imp/Cln) • High-dose isoniazid (high-dose H)[b] • Clarithromycin (Cls)

[a] Adapted from reference 24.

[b] high-Dose isoniazid is defined as 16-20 mg/kg/ day. Some experts feel that high-dose isoniazid can still be used in the presence of resistance to low concentrations of isoniazid (>1% of bacilli resistant to 0.2 μg/ml but susceptible to 1 μg/ml of ispniazid), whereas isoniazid is not recommended for hugh-dose resitance (>1% of bacilli resistant to 1 μg/ml of isoniazid).

Table 5. General principles for designing MDR-TB treatment regimens [a].

Principles	Comments
1. Use at least 4 drugs certain to be effective	The more of the following factors are present, the more likely it is that the drug will be effective: • Resistance to these drugs is known from surveys to be rare in similar patients. • DST results show susceptibility to drugs for which there is good laboratory reliability: injectable agents and fluoroquinolones. • The drug is not commonly used in the area • (For decisions about an individual patient-no prior history of treatment failure with the drug; no known clise contacts with resistance to the drug.)
2. Do not use drugs for which there is the possibility of cross-resistance	• Many antituberculosis agents exhibit cross-resistance both within and across drug classes
3. eliminate drugs that are not safe	• Quality of the drug is unknown. • (For decisions about an individual patient-known severe allergy or unmanageable intolerance: high risk of severe adverse drug effects such as renal failure, deafness, hepatitis, depression and/or psychosis.)
4. include drugs from groups 1-5 in a hierarchical order based on potency	• Use any of the first-line oral agents (Group 1) that are likely to be effective • Use an effective aminoglycoside or polypeptide by injection (Group2). [b] • Use a fluoroquinolone (group 3). • Use the remaining Group 4 drugs to complete a regimen of at least four effective drugs. • For regimens with fewer than four effective drugs, consider adding two Group 5 drugs. The total number of drugs will depend on the degree of uncertainly, and regimens often contain five to seven.

[a] Adapted reference 24.

[b] Avoid streptomycin even if DST suggest susceptibility because if high rates of resistance with resistant TB strains and higher incidence of ototoxicity.

The followings are the important adverse effects of medications that may occur during the course of MDR-TB treatment (23, 24):

1- Convulsion: It is a side effect of cycloserine or isoniazid and if occurs, the responsible drug should be stopped. Convulsion treatment (with phenytoin or valproic acid) should be initiated and dosage of pyridoxine (B6) has to be increased by 200 mg daily. After recovery, treatment with cycloserine should be restarted at a low dose with gradual increase in dosage until reaching the conventional dosage form (23, 24). Consultation with a neurologist is necessary in such cases.

*Anti-convulsion medication should be continued till the end of MDR-TB treatment course.

*Previous history of convulsion is not a contraindication for the drug usage.

2- Peripheral neuropathy: It may develop as a side effect of isoniazid, cycloserine, amikacin, prothionamide and ofloxacin. If this complication occurs, pyridoxine (B6) dosage is increased to 200 mg daily. Nortriptyline or gabapentin can be administered to reduce the symptoms (23, 24).

3- Hearing loss and vestibular disorders: Injectable drugs (amikacin and capreomycin) are the most common cause of these complications. In case of occurrence, audiometry needs to be done. If the complication is confirmed, considering the necessity of amikacin to be in the drug regimen, its administration should be decreased to 3 times a week (24).

4- Psychosis: It may be a side effect of cycloserine, isoniazid or prothionamide and if occurs, psychiatric consultation is essential. Responsible drugs have to be discontinued for a period of 1-4 weeks and anti-psychotic medications have to be initiated.

*Anti-psychotic medications should continue throughout the course of MDR-TB treatment.

*History of previous mental disorders is not a contraindication for administration of these drugs (23, 24).

5- Depression: It may develop due to the administration of cycloserine, isoniazid or prothionamide. If depression occurs, psychiatric counseling is required and efforts must be made to improve the patient's quality of life. Anti-depressants need to be started and dosage of the responsible drug has to be diminished if possible (consultation with MDR-TB specialists is necessary)(23, 24).

6- Hypothyroidism: It may be a side effect of PAS or ethionamide and if develops, levothyroxine should be started (23, 24).

7- Nausea and vomiting: These complications mostly occur during the first weeks following initiation of therapy and are resolved by symptomatic treatment. In case of severe vomiting, serum electrolytes have to be checked (23, 24).

8- Gastritis: It is a side effect of PAS and prothionamide. If this complication occurs, the responsible drugs should be stopped for 1-7 days and H2 blockers or omeprazole have to be started (23, 24).

9- Hepatitis: It is a side effect of prothionamide, PAS, pyrazinamide and quinolones. If this complication occurs, the whole treatment has to be suspended and after the recovery and resolution of symptoms, hepatotoxic medications will be added to the regimen one by one (23, 24).

10- Nephrotoxicity: It is a side effect of injectable drugs (aminoglycosides). In case of occurrence, the responsible drugs have to be discontinued and dosage of other medications must be modified based on the serum level of creatinine (23, 24). If the patient is stable, aminoglycosides may be initiated 2 to 3 times a week.

11- Hypokalemia and hypomagnesaemia: If the potassium serum concentration is low, magnesium serum level also needs to be checked. If serum levels of electrolytes are low, they have to be replaced (23, 24).

12- Arthralgia: It is a side effect of quinolones which is usually resolved by the continuation of treatment. If this complication continues, pain relievers may be prescribed (23, 24).

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