Prevention & Management of Adverse Reactions associated with Antitubercular Drugs

Patient Guide,
Ready Reckoners for Health Workers and Medical Officers
and Reference Manuals for Medical Officers and Specialists

Indian Council of Medical Research, Ministry of Health & Family Welfare, New Delhi

Central TB Division, Directorate General of Health Services, Ministry of Health & Family Welfare, Nirman Bhawan, New Delhi

2016

Prevention & Management of Adverse Reactions associated with Antitubercular Drugs

Patient Guide,
Ready Reckoners for Health Workers and Medical Officers
and Reference Manuals for Medical Officers and Specialists

By:
Indian Council of Medical Research; Ministry of Health & Family Welfare, New Delhi
Central TB Division; Directorate General of Health Services, Ministry of Health & Family Welfare, Nirman Bhawan, New Delhi
Government of India

March 2016

Suggestions and comments that will improve the document and its use are welcome.

Limitation of liability / Disclaimer of warranty

All reasonable precautions have been taken while preparing this document. The contents in this publication are based on published literature, data from Pharmacovigilance Program of India (PvPI) and personal experience of experts.

It is intended as a guidance document and should be used for the benefit of the patients. All efforts will be made in future to update this publication as and when new information of relevance or new drugs are made available in RNCTP, however user should refer to most current information while interpreting and using this document. ICMR and CTD will not be responsible for any issues arising from the use of information in this publication.

Contents

Acknowledgement

Freedom from TB is possible with timely, regular and complete treatment with anti TB drugs.

Although National TB Control Program provides guidelines, due to misunderstanding about side effects, many patients do not take treatment properly, suffer even more with worsening of disease, development of resistance and need for more expensive and prolonged treatment.

Hence it was felt that there is need to explain to patients the side effects, specially early symptoms and precautions to be taken for preventing side effects and emphasize the importance of early reporting to nurses, doctors, specialists for managing side effects. This is particularly relevant now, as with rising resistance we are using second line drugs and daily treatment regimen which have greater potential for side effects.

With the initiative of Indian Council of Medical Research (ICMR) and Central TB Division (CTD), these guidelines, ready reckoners and manuals for preventing and managing side effects have been developed for patients, health workers, doctors and specialists. The guidelines have been conceptualized, written, reviewed and edited by experts, (in alphabetical order) Dr. Abdus Samad, Dr. Akhilesh Chamediya, Dr. Amar Shah, Dr. Anish Sule, Dr. B. Rajagopalan, Dr. Basanta Hazarika, Dr. D. Behera, Dr. Deepa Arora, Dr. G. N. Singh, Dr. Ivona Lobo, Dr. J. K. Samaria, Dr. Jagdish Prasad, Dr. Jaylaxmi Nalawade; Dr. Jyotsna M Joshi; Dr. K. S. Sachdeva; Dr. Manjula Singh; Dr. Nilima A. Kshirsagar, Dr. Padmapriya, Dr. Rajendra Prasad, Dr. Rajendra Singh Chouhan, Dr. Rajni Kaul, Dr. Rashmi Arora, Dr. Rupak Singla, Dr. S. K. Sharma, Dr. Soumya Swaminathan, Dr. Srikanth Tripathy, Dr. Sunil Khaparde, Dr. V. Kalaiselvan, Dr. Vijay Kumar, Dr. Y. K. Gupta, facilitated and printed by M/S Lupin which is gratefully acknowledged.

Invaluable guidance and support from Dr. Soumya Swaminathan Secretary Department of Health Research, Director General Indian Council of Medical Research and Dr. Jagdish Prasad Director General Health Services Ministry of Health & family welfare Government of India is gratefully acknowledged.

We also acknowledge with gratitude numerous patients, health workers and doctors who have fought with conviction and courage the scourge of tuberculosis and helped in bettering the lives of others.

March 2016

Abbreviations

ADR	:	Adverse drug reaction
AG	:	Aminoglycosides
ALT	:	Alanine aminotransferase
ANCA	:	Anti-neutrophil cytoplasmic antibody
AST	:	Aspartate aminotransferase
BD	:	Bis in Die
BSA	:	Body surface area
CrCL	:	Creatinine clearence
CT	:	Computed Tomography
CTD	:	Central TB division
CYP	:	Cytochrome
dL	:	decilitre
ECG	:	Electrocardiogram
EMB	:	Ethambutol
FNAC	:	Fine needle aspiration cytology
FQ	:	Fluoroquinolones
g	:	gram
HIV	:	Human immunodeficiency virus
ICMR	:	Indian Council of Medical Research
INH	:	Isoniazid
IU	:	International unit
IUD	:	Intra-uterine device
IV	:	Intravenous
kg	:	Kilogram
L	:	Litre
LFT	:	Liver function test
MAO	:	Monoamine oxidase
mg	:	Miligram
min	:	Minutes

Abbreviations

mm	:	Milimeter
ms	:	Miliseconds
NIRT	:	National Institute for Research in Tuberculosis
NSAIDs	:	Non-steroidal anti-inflammatory drugs
OCP	:	Oral contraceptive pill
OD	:	Once daily
ORS	:	Oral rehydration solution
PAS	:	Para-amino salicylic acid
PZA	:	Pyrazinamide
PvPI	:	Pharmacovigilance Program of India
RFT	:	Renal function test
RIF	:	Rifampicin
RNTCP	:	Revised National Tuberculosis Control Program
SGOT	:	Serum glutamic oxaloacetic transaminase
SGPT	:	Serum glutamic pyruvic transaminase
SLE	:	Systemic lupus erythematosus
TB	:	Tuberculosis
TdP	:	Torsades de pointes
TSH	:	Thyroid stimulating hormone
ULN	:	Upper normal limit

The terms adverse drug reactions (ADRs), adverse reactions and side effects are used synonymously in this document for simplicity.

Introduction

Freedom from TB is possible with timely, regular, complete treatment, with reassurance and prevention and management of side effects of antitubercular drugs.

Although Information on monitoring and management of side effects of anti TB drugs has been provided in the general guidelines of National TB Control Program, it is seen that many patients don't complete treatment due to misunderstanding about side effects. They develop resistance and suffer due to worsening of disease and require more costly and prolonged treatment.

It was realised that there is a need to inform patients, health workers and doctors, ways and means of recognizing early signs and symptoms, preventing and managing side effects, specially as the program now includes use of second line drugs and daily treatment with first line drugs, which are likely to cause more side effects.

With ICMR initiative and support from CTD, the guidance chart for patients, ready reckoners for health workers and doctors and reference manuals for doctors and specialists have been prepared by experts, importantly giving practical guidelines based on experience in India.

The documents provide general instructions, reiterating importance of nutritious diet, completing full course of treatment, preventing, reporting, managing side effects early, dangers of smoking, alcohol and self-medication.

The patient guide in English, Hindi and in regional languages (under preparation) gives with pictorial illustration specific information on side effects like (nausea, jaundice, tingling and numbness) ways and means of preventing and managing these.

The ready reckoner for health workers gives in an easy to understand tabular form side effects, drugs that are causative and action to be taken by the health workers such as reassurance and management e.g. take drug in banana if nausea, ORS if diarrhea, and immediate referral for jaundice.

The ready reckoner for doctors, provides in table form, clinical features, diagnosis, suspect drugs, differential diagnosis/other causes, methods of prevention and

management and indications for referral to specialist. Specific instructions are provided when to stop and when and how to restart anti TB drugs. Guidance on management in pregnant and nursing women is also provided.

In separate manuals for general practitioners and specialists we provide in great detail, side effects of first line, second line and class V drugs, signs, symptoms and specific organs involved, timelines of occurrence, lab tests to evaluate, prevent, diagnose early and manage side effects

The manual for specialists gives in section 1, for 17 main Adverse Drug Reactions (ADRs), detailed information and guidelines on causative drugs, clinical presentations, frequency, time of onset, reversibility, progression, diagnosis, management, risk factors, precautions and measures to prevent, with Indian data and references.

In the next section, for 15 antitubercular drugs, drug wise ADRs, clinical presentation, time to onset, severity, management, contraindications, interaction with other drugs, food, common medication errors, use in special population, are provided with references. In appendices, specific aspects of some side effects such as jaundice, other drugs causing similar side effects, laboratory tests, use of anti TB drugs in HIV, management of pregnancy and lactation, drugs for treating common side effects is provided.

The Pharmacovigilance Program of India (PvPI) has been collecting ADRs reported by practitioners, health workers and patients. Recently it has developed links with RNTCP, we have provided a summary of ADRs received by PvPI.

We plan to update this document in future as new information becomes available, new drugs are introduced and feedback we get from you. Your queries, suggestions, feedback regarding this manual can be communicated to National Institute for Research in Tuberculosis (NIRT) at darsini69@hotmail.com and to ddgtb@rntcp.org, which will help to further improve the document and its use.

Prevention & Management of Adverse Reactions associated with Antitubercular Drugs

Patient Guide (English)

Indian Council of Medical Research, Ministry of Health & Family Welfare, New Delhi

Central TB Division, Directorate General of Health Services, Ministry of Health & Family Welfare, Nirman Bhawan, New Delhi

2016

Important information:

- Not everyone gets side effects.
- If you get side effects, inform and consult your doctor / nurse
- Early action prevents side effects
- Some symptoms may be experienced due to other causes and need investigation
- **Don't stop your drugs or restart them on your own.**
- **Don't share your drugs or advice treatment to others.**
- **Don't smoke or drink alcohol as it can worsen side effects**

Main Adverse Reactions:

Nausea / Vomiting

- Can be due to TB drugs causing stomach irritation
- Take drugs embedded in banana
- Avoid smoking and drinking alcohol
- Eat nutritious food
- Inform and consult your doctor / nurse

Loss of appetite
Pain / discomfort in abdomen
Yellow skin, yellow eyes, dark colored urine

- Can be due to TB drugs
- May indicate harm to liver
- Inform and consult your doctor / nurse immediately

Note: Orange coloration of urine is due to Rifampicin

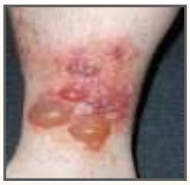
Tingling, burning, numbness in hands & feet

- Can be due to TB drugs causing neuropathy
- Inform and consult your doctor / nurse
- Can be prevented by taking vitamin B6 on doctor's advice

Flu like symptoms:
Chills, body ache, shortness of breath
Tiredness, dry cough
Loss of appetite

- Can be due to Rifampicin
- Usually mild and subsides on its own
- May be due to flu infection. Inform and consult your doctor / nurse

Itching and Rash



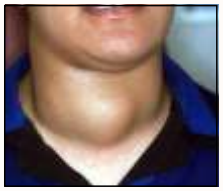
- Can be due to TB drugs causing skin reactions
- If rash develops in the mouth or nose or involves very large body area or is associated with fever; inform and consult your doctor / nurse immediately

Reduced vision
Any problem in the eye
Can be due to Ethambutol
- Inform and consult your doctor / nurse immediately
- Usually resolves on stopping Ethambutol
- If Ethambutol is stopped, it needs to be replaced by another drug to fully treat TB

Pain in joints, muscles, tendons
Difficulty in movements
- Can be due to Pyrazinamide and Fluroquinolones
- Usually harmless
- Can be treated with pain killers
- Inform and consult your doctor / nurse immediately

Diminution or loss of hearing
Ringing in ears
Giddiness
Loss of balance
- Can be due to some TB drugs
- Inform and consult your doctor / nurse immediately

Slowness of activities
Swelling of face
Swelling in neck
Disproportionate weight gain
- Can be due to thyroid dysfunction caused by PAS or Ethionamide
- Inform and consult your doctor / nurse



Tiredness, Lethargy
Headache
Pale look
Palpitations
- Can be due to anemia caused by some TB drugs
- Inform and consult your doctor / nurse
- Needs to be evaluated and can be treated with nutritious food and appropriate drugs

---

Convulsion
Feeling low in mood
Seeing abnormal things
Suicidal or abnormal thoughts
- Can be due to some TB drugs.
- Inform and consult your doctor / nurse immediately.

Prevention & Management of Adverse Reactions associated with Antitubercular Drugs

Patient Guide (Hindi)

Indian Council of Medical Research, Ministry of Health & Family Welfare, New Delhi

Central TB Division, Directorate General of Health Services, Ministry of Health & Family Welfare, Nirman Bhawan, New Delhi

2016

महत्त्वपूर्ण जानकारी :

- सभी मरीजोंको दुष्प्रभाव नहीं होते।
- यदि आपको दुष्प्रभाव होते हैं, तो अपने डॉक्टर/नर्स को सूचित करें एवं उनकी सलाह लें।
- जल्दी कार्यवाही से दुष्प्रभाव से बचा जा सकता है।
- कुछ लक्षण अन्य कारणों की वजह से हो सकते हैं और इन्हें जाँच की आवश्यकता है।

- **अपनी दवाईयों को स्वयं ही बंद या चालू न करें।**
- **अपनी दवाईयाँ इतरोंको ना दे या दूसरों को उपचार की सलाह न दें।**
- **धूम्रपान न करें व शराब न पीएँ क्योंकी इससे दुष्प्रभाव और बढ़ सकते हैं।**

मुख्य दुष्प्रभाव:

मतली / उल्टी

- टीबी की दवाईयों की वजह से पेट में जलन के कारण हो सकता है
- दवाओं को केले में सन्निहित करके लें
- धूम्रपान न करें और शराब न पीएँ
- पौष्टिक खाना खाएँ
- अपने डॉक्टर/नर्स को सूचित करें और उनकी सलाह लें

भूख में कमी

पेट में दर्द/बेचैनी

पीली त्वचा, पीली आँखे, गहरे रंग का मूत्र

- टीबी की दवाईयों की वजह से हो सकता है
- यह जिगर की क्षति/लिवर की विषाक्तता दर्शाता है
- तत्काल अपने डॉक्टर/नर्स को सूचित करें और उनसे सलाह लें

सुचना : नारंगी रंग का मूत्र रिफैम्पिसिन की वजह से हो सकता है

हाथों और पैरों में झुनझुनी, जलन, सुन्नता

- यह टीबी की दवाईयों के कारण होने वाली न्यूरोपैथी की वजह से हो सकता है
- अपने डॉक्टर/नर्स को सूचित करें और उनकी सलाह लें
- डॉक्टर की सलाह पर विटामिन बी6 लेने से इस का निवारण हो सकता है

फ्लू जैसे लक्षण :

ठंड लगना, शरीर में दर्द, साँस फुलना

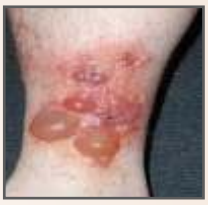
थकान, सूखी खाँसी

भूख में कमी

- यह रिफैम्पिसिन की वजह से हो सकता है
- आमतौर पर मामूली होता है और अपने आप कम हो जाता है
- यह फ्लू के संक्रमण की वजह से भी हो सकता है। अपने डॉक्टर/नर्स को सूचित करें और उनकी सलाह लें

खुजली / दाने / चकत्ते

- टीबी की दवाईयों की वजह से हो सकते है
- यदि मुँह या नाक में या शरीर के बहुत बड़े क्षेत्र में होता हैं या बुखार भी आता है; तो तत्काल अपने डॉक्टर/नर्स को सूचित करें और उनकी सलाह लें



कम दिखाई देना

आँखों में कोई समस्या

- यह इथेमब्यूटोल की वजह से हो सकता है
- अपने डॉक्टर/नर्स को तुरंत सूचित करें और उनकी सलाह लें
- आमतौर पर इथेमब्यूटोल को बंद करने पर इसका निराकरण हो जाता है
- यदि इथेमब्यूटोल को बंद कर दिया जाता है, तो टीबी का पूरी तरह इलाज करने के लिए उसकी जगह पर अन्य दवा शुरू करने की आवश्यकता है

जोड़ों, मांसपेशियों, स्नायु में दर्द

चलने में या हिलने में कठिनाई

- यह पायराझिनामाइड और फ्लोरोक्विनोलोन के कारण हो सकता है
- आमतौर पर हानिरहित
- इनका दर्दनाशक दवाओं द्वारा इलाज किया जा सकता है
- तुरंत अपने डॉक्टर/नर्स को सूचित करें और उनकी सलाह लें

सुनने की क्षमता में कमी या ह्रास

घंटी बजने जैसी आवाजें सुनने देना

चक्कर आना

संतुलन में कमी

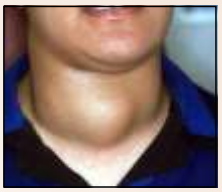
- यह टीबी की दवाईयों की वजह से हो सकता है
- तत्काल अपने डॉक्टर/नर्स को सूचित करें और उनकी सलाह लें

सुस्ती

चेहरे पर सूजन

गर्दन में सूजन

असामान्य रुप से वजन बढ़ना



- यह इथीओनएमाइड या PAS की वजह से होने वाले थायराइड रोग के कारण हो सकता है
- अपने डॉक्टर/नर्स को सूचित करें और उनकी सलाह लें

थकान, सुस्ती

सिरदर्द

कांतिहीन चेहरा

घबराहट

- कुछ टीबी की दवाओं की वजह से होने वाली खून की कमी (एनीमिया) के कारण हो सकता है
- अपने डॉक्टर/नर्स को सूचित करें और उनकी सलाह लें
- इसकी जाँच करनी चाहिए, इसका इलाज, पौष्टिक भोजन और उचित दवाओं से किया जा सकता है

दौरा पड़ना

मूड खराब होना

आवाजे सुनाई देना

चित्रविचित्र वस्तुएँ दिखना

आत्मघाती विचार

- टीबी की कुछ दवाईयों की वजह से हो सकता है
- तत्काल अपने डॉक्टर/नर्स को सूचित करें और उनसे सलाह लें

Prevention & Management of Adverse Reactions associated with Antitubercular Drugs

Ready Reckoner for Health Workers (English)

Indian Council of Medical Research, Ministry of Health & Family Welfare, New Delhi

Central TB Division, Directorate General of Health Services, Ministry of Health & Family Welfare, Nirman Bhawan, New Delhi

2016

Side effects associated with anti-TB drugs and their prevention and management

Important general instructions:

1. Ensure that patient completes full course of anti-TB therapy
2. Side effects of anti-TB drugs can be an important cause of patient stopping medication, especially with second line drugs
3. Prevention and early detection of side effects are needed
4. Alcohol, smoking and use of illicit drugs increase side effects
5. Relevant history, clinical examination and lab tests are important to evaluate risk factors and diagnosis of side effects at an early stage
6. For contraception, ask patient to seek advice from family planning center as oral contraceptives are less effective with some anti-TB drugs
7. Educate, counsel and reassure patients for self-limiting side effects
8. Side effects and serious side effects requiring immediate action ⟶ **refer patients to Medical officer**
9. Report serious side effects to PvPI center (Procedure for reporting: Call your nearby PvPI center and provide complete information about side effect. Contact details of the nearest PvPI center are: Name of the Centre - _____; Contact no: _____; National toll free number: **1800 180 3024**)
10. Advice nutritious diet to TB patients
11. Advice patients about respiratory hygiene and provide information on preventing spread of TB (Cover nose and mouth with facemask, tissue paper)

Table 1: Some common and rare side effects of anti-TB drugs are as follows:

Common (Seen in 1-10% patients)	Rare (Seen in less than 1% patients)
Nausea, Vomiting, Gastritis, Hepatitis, Hypersensitivity reactions, Cutaneous reactions	Flu like syndrome, Peripheral neuropathy, Ocular toxicity, Dysglycemia, Gynaecomastia, Hypothyroidism, Joint related side effects, Tendinopathy and tendinitis, Myelosuppression, Anaemia, Thrombocytopenia, Psychosis, Seizures, Prolongation of QT interval

Table 2: Symptoms, causative drugs and action to be taken by Health worker:

Symptoms	Which drugs cause	Action by Health Workers
Upper abdominal pain - Frequent	All oral anti-TB drugs	Indicates **gastritis.** Advise patients to increase fluid intake. Patients should not take antacids / acid lowering agents together with first line anti-TB drugs as it reduces the absorption of drugs. **Refer to Medical Officer**.
Nausea, vomiting	All oral anti-TB drugs	Reassure patient. Advice patient to take drugs embedded in a banana. Give drugs with less water and over a longer period of time (e.g. 20 minutes). However, later in the day, patients should take sufficient water. **If above measures fail, refer to Medical Officer.**
Nausea, vomiting with yellowness of skin and dark colour urine	Mainly by Pyrazinamide, Rifampicin and Isoniazid	Indicates **Liver toxicity**. Refer to Medical officer urgently.

Symptoms	Which drugs cause	Action by Health Workers
Loose motions >4 times, liquid stools	Mainly by PAS, Ethionamide, Isoniazid, Rifampicin, Ofloxacin, Levofloxacin, Moxifloxacin	Counsel patients on food and personal hygiene. Advice 200 ml Oral rehydration solution (ORS) after every loose stool to maintain hydration. **Refer to Medical officer**.
Loose motions associated with dryness of skin and mouth, decreased urination, tiredness and sunken eyes	Same as above	Indicates **Dehydration** (Serious) Refer to Medical officer urgently
Itching / Rashes	Mainly by Ethambutol, Rifampicin, Streptomycin	Reassure patient. **If rash persists, refer to Medical Officer**.
Itching / Rashes involving very large body area or present in mouth, nose associated with swelling and fever	Mainly by Ethambutol, Rifampicin, Streptomycin	Indicates systemic involvement (Serious) Refer to Medical officer urgently
Tingling /burning /numbness in hands and feet	Mainly Isoniazid, Cycloserine	Check that patient is taking Pyridoxine. **Refer to Medical officer.**
Pain in Joints	Mainly Pyrazinamide	Paracetamol can be given if only 1-2 joints are involved. Reassure patient that it is a self-limiting condition. If > 2 joints are involved or pain is not relieved, **refer to Medical officer.**
Impaired vision: Pain, Blurring of vision, Disturbance in color vision	Mainly Ethambutol	Indicates **Eye toxicity**. Refer to Medical officer urgently

Symptoms	Which drugs cause	Action by Health Workers
Flu-like syndrome: Chills, dry cough, shortness of breath, loss of appetite, body ache, malaise	Mainly Rifampicin	Reassure patient. If not controlled, refer patient to **Medical Officer** for evaluation.
Swelling of face or legs, less or no urine	Amikacin, Kanamycin, Capreomycin, Streptomyin	Indicates **Kidney toxicity**. Refer to Medical officer urgently
Seeing abnormal things, change of thoughts, suicidal thoughts	Mainly Cycloserine	Indicates **Psychiatric disturbances**. Refer to Medical officer urgently
Tiredness, lethargy, headache, giddiness, pale look, palpitations	Mainly Linezolid, Isoniazid, Rifampicin, Pyrazinamide, Ofloxacin, Levofloxacin, Moxifloxacin	Indicates **Anemia**. Patients can be advised rest in DOTS center post-dosing to avoid giddiness. Advice patients on nutrition Refer **to Medical Officer** for evaluation.
Ringing in ears, Loss of hearing, dizziness and loss of balance leading to recurrent fall	Mainly Streptomycin, Amikacin, Kanamycin, Capreomycin	Indicates **Ear toxicity**. Refer to Medical officer urgently
Slowness of activities, swelling of face, swelling in neck, disproportionate weight gain	Mainly PAS and Ethionamide	Indicates **Thyroid involvement**. Refer to Medical officer urgently
Pain and swelling in muscles and Tendons, difficulty in movement	Ofloxacin, Levofloxacin and Moxifloxacin	Indicates **Tendonitis**. Refer to Medical officer urgently
Seizure: Convulsion	Isoniazid, Cycloserine, Ofloxacin, Levofloxacin, Moxifloxacin	Refer to Medical officer urgently
Orange and reddish color of urine sweat, phlegm (sputum), saliva or tears may be noticed. As this is quite common with rifampicin, reassure patients.		

Prevention & Management of Adverse Reactions associated with Antitubercular Drugs

Ready Reckoner for Health Workers (Hindi)

Indian Council of Medical Research, Ministry of Health & Family Welfare, New Delhi

Central TB Division, Directorate General of Health Services, Ministry of Health & Family Welfare, Nirman Bhawan, New Delhi

2016

टीबी की दवाईयों से जुड़े हुए दुष्प्रभाव और उनका प्रबंधन एवं निवारण

महत्त्वपूर्ण सूचना :

१. यह सुनिश्चित करें कि मरीज टीबी (क्षयरोग) की सम्पूर्ण चिकित्सा लें।

२. टीबी की दवाओं को बताये गए तरीके से ना लेने या बीच मे छोड़ने का कारण टीबी की दवाओं के दुष्प्रभाव (साइड इफेक्ट) है। विशेषत: यह दूसरी पंक्ति (सेकंड लाइन) की टीबी दवाओं के साथ हो सकता है।

३. दवाओं के दुष्प्रभावों (साइड इफेक्ट) को रोकना और जल्दी पता लगाना जरूरी है।

४. शराब, धूम्रपान और अवैध दवाओं के व्यसन से टीबी की दवाओं के दुष्प्रभाव (साइड इफेक्ट) बढ़ते हैं।

५. दवाओं के दुष्प्रभावों (साइड इफेक्ट) के कारणों का शुरुवाती दौर में ही पता लगाने और उपचार के लिए, मरीज के अन्य रोग और स्वास्थ्य संबंधी जानकारी, चिकित्सकीय जाँच और प्रयोगशाला जाँच (लैब टेस्ट) जरुरी हैं।

६. चूँकि टीबी की दवाओं के साथ गर्भ निरोधक गोलियों का असर कम हो जाता है, अत: मरीजों को गर्भ निरोध के लिए कुटुंब नियोजन केंद्र से सलाह लेने के लिऐ कहें।

७. जो दुष्प्रभाव (साइड इफेक्ट) स्वयं खत्म हो जाते हैं उनके बारे में मरीजों को शिक्षित और आश्वस्त करें।

८. वो दुष्प्रभाव (साइड इफेक्ट) जिनके लिए तत्काल कार्रवाई की आवश्यकता हो ⟶ मरीज को चिकित्सा अधिकारी के पास भेजें।

९. गंभीर दुष्प्रभाव (सीरियस साइड इफेक्ट) PvPI केंद्र को रिपोर्ट करें। (**PvPI केंद्र को रीपोर्ट करने की विधी:** नजदीकी PvPI केंद्र को फोन करें एवं उन्हें सीरियस साइड इफेक्ट की पूरी जानकारी दें। नजदीक PvPI केंद्र का नाम ....., फोन नंबर ..... राष्ट्रीय टोल फ्री नंबर **१८०० १८० ३०२४**)

१०. टीबी रोगियों को पौष्टिक आहार लेने की सलाह दें।

११. रोगियों को सांस संबंधी स्वच्छता बनाये रखने और टीबी के प्रसार को रोकने के तरीकों, जैसे कि फेसमास्क या टिश्यू से चेहरे को ढकना आदि की जानकारी दें।

टेबल १: क्षयरोग की दवाओं के आम और दुर्लभ दुष्प्रभाव :

आम (Common) (१-१०% मरीजों में होते हैं)	दुर्लभ (Rare) (1% से कम मरीजों में होते है)
मतली और उल्टी, जठरशोध (गैस्ट्राइटिस), हेपेटाइटिस; अतिसंवेदनशीलता प्रतिक्रिया; त्वचा की प्रतिक्रिया (त्वचा पर दाने और खुजली)	सर्दी जुकाम जैसे लक्षण; परिधीय न्यूरोपैथी, नेत्र विषक्तता, ग्लूकोस का कम या ज़्यादा होना, गायनेकोमेस्टिआ, हाइपोथायरायडिज्म, जोड़ों की समस्या, स्नायु विकार, मायलोसप्रेशन, खून की कमी (एनीमिया), थ्रोम्बोसाइटोपेनिया, मनोविकृति, दौरा पड़ना, ECG में QT अंतराल का बढना

टेबल २: लक्षण, हानिकारक दवाएं और स्वास्थ्य कार्यकर्ताओं द्वारा कार्रवाई

लक्षण	हानिकारक दवाएं	स्वास्थ्य कार्यकर्ताओं द्वारा कार्रवाई
पेट के ऊपरी हिस्से में बारबार दर्द होना	मुंह से लेने वाली टीबी की सभी दवाएं	रोगियों को तरल पदार्थों का सेवन बढाने की सलाह दें । मरीजों को पहली पंक्ति (फर्स्ट लाइन) की टीबी दवाओं के साथ antacids (पेट की जलन कम करने वाली दवाएं) नहीं लेना चाहिए, यह दवाओं के अवशोषण को कम कर देता है । चिकित्सा अधिकारी से संपर्क करें और मरीज़ को चिकित्सा अधिकारी से जांच के लिए भेजें ।
मतली और उल्टी	मुंह से लेने वाली टीबी की सभी दवाएं	दवाओं को कम पानी के साथ और लंबी अवधि (उदाहरण के लिए २० मिनट) में दे । हालांकि, बाद में दिन में, मरीज को पर्याप्त पानी लेना चाहिए । सुधार ना हो तो मरीज को टीबी की दवाएं केले में लेने की सलाह दें और आश्वस्त करें । चिकित्सा अधिकारी से संपर्क करें और मरीज़ को चिकित्सा अधिकारी से जांच के लिए भेजें ।
उल्टी,मतली के साथ त्वचा का पीलापन और गहरे रंग का पेशाब	मुख्य रूप से पायराजिनामाइड, रिफेम्पसिन, आइसोनिआज़िड	**लिवर की विषाक्तता** को दर्शाता है । तत्काल चिकित्सा अधिकारी से संपर्क करें और मरीज को चिकित्सा अधिकारी से जांच के लिए भेजें ।

लक्षण	हानिकारक दवाएं	स्वास्थ्य कार्यकर्ताओं द्वारा कार्रवाई
४ बार से ज्यादा पतले दस्त	PAS, एथिओनामाइड आइसोनिआज़िड, रिफेम्पसिन, ओफ्लोक्सासिन, लिवोफ्लोक्सासिन, मोक्सीफ्लोक्सासिन	भोजन और व्यक्तिगत स्वच्छता पर रोगियों को परामर्श दें। शरीर में पानी की कमी पूरी करने के लिए दस्त के बाद २०० मिलीलीटर ओरल रिहाइड्रेशन घोल-ORS पीने की सलाह दें। चिकित्सा अधिकारी से संपर्क करें और मरीज को चिकित्सा अधिकारी से जांच के लिए भेजें।
दस्त के साथ त्वचा और मुँह का सूखापन, पेशाब कम होना और आँखें धंसना	ऊपर लिखी टीबी की दवाएं	यह शरीर में पानी की कमी को दर्शाता है (गंभीर)। तत्काल चिकित्सा अधिकारी से संपर्क करें और मरीज को चिकित्सा अधिकारी से जांच के लिए भेजें।
खुजली/चकत्ते	मुख्य रुप से एथम्बुटोल, रिफेम्पसिन, स्ट्रेप्टोमायासिन	रोगी को आश्वस्त करें। अगर चकत्ते बने रहते हैं तो चिकित्सा अधिकारी से संपर्क करें और मरीज को चिकित्सा अधिकारी से जांच के लिए भेजें।
शरीर के बहुत बड़े भाग में या मुँह और नाक में खुजली/चकत्ते एवं सूजन या बुखार	मुख्य रुप से एथम्बुटोल, रिफेम्पसिन, स्ट्रेप्टोमायासिन	पूरे शरीर में फैलने का संकेत (गंभीर)। तत्काल चिकित्सा अधिकारी से संपर्क करें और मरीज को चिकित्सा अधिकारी से जांच के लिए भेजें।
हाथों और पैरों में झुनझुनी /जलन/सुन्न होना	मुख्य रुप से आइसोनिआज़िड, सायक्लोसरीन	जाँच करें कि मरीज पायरीडॉक्सिन निर्देशानुसार ले रहा है। चिकित्सा अधिकारी से संपर्क करें और मरीज को चिकित्सा अधिकारी से जांच के लिए भेजें।
जोड़ों में दर्द	मुख्य रुप से पायराजिनामाइड	यदि सिर्फ १-२ जोडों में दर्द हो तो पेरासिटामोल का उपयोग करें। यदि दर्द स्वयं ख़त्म हो जाए तो मरीज को आश्वस्त करें। यदि दर्द २ से ज्यादा जोडों में हो या दर्द से राहत ना हो तो चिकित्सा अधिकारी से संपर्क करें और मरीज को चिकित्सा अधिकारी से जांच के लिए भेजें।

लक्षण	हानिकारक दवाएं	स्वास्थ्य कार्यकर्ताओं द्वारा कार्रवाई
आँखों में दर्द, धुंधला दिखना, रंग की पहचान में बाधा आना	मुख्य रुप से एथम्बुटोल	**नेत्र विषाक्तता** को दर्शाता है । तत्काल चिकित्सा अधिकारी से संपर्क करें और मरीज को चिकित्सा अधिकारी से जांच के लिए भेजें।
सर्दी जुकाम जैसे लक्षण: ठंड लगना, सूखी खांसी, साँस फूलना, भूख न लगना, शरीर में दर्द, बैचेनी	मुख्य रुप से रिफेम्पसिन	मरीज को आश्वस्त करें। यदि लक्षण ठीक ना हो तो चिकित्सा अधिकारी से संपर्क करें और मरीज को चिकित्सा अधिकारी से जांच के लिए भेजें।
चेहरे या पैरों में सूजन, पेशाब कम होना या ना होना	अमिकासिन, केनामायसिन, केप्रेओमाइसिन, स्ट्रेप्टोमायासिन	**किडनी की विषाक्तता** को दर्शाता है । तत्काल चिकित्सा अधिकारी से संपर्क करें और मरीज को चिकित्सा अधिकारी से जांच के लिए भेजें।
असामान्य चीजें दिखना, विचार में परिवर्तन, आत्महत्या के विचार	मुख्य रुप से सायक्लोसरीन	**मनोरोग** को दर्शाता है । तत्काल चिकित्सा अधिकारी से संपर्क करें और मरीज को चिकित्सा अधिकारी से जांच के लिए भेजें।
थकान, सुस्ती, सिर दर्द, चक्कर आना, कांतिहीन चेहरा, घबराहट	मुख्य रुप से लिनेज़ोलिड, आइसोनिआज़िड, रिफेम्पसिन, पायराजिनामाइड, ओफ्लोक्सासिन, लिवोफ्लोक्सासिन, माक्सीफ्लोक्सासिन	**एनीमिया** को दर्शाता है । रोगियों को चक्कर से बचने के लिए दवा की खुराक के बाद डॉट्स केंद्र में आराम की सलाह दी जा सकती है। मरीज को आहार सम्बन्धी सलाह दें। चिकित्सा अधिकारी से संपर्क करें और मरीज को चिकित्सा अधिकारी से जांच के लिए भेजें।

लक्षण	हानिकारक दवाएं	स्वास्थ्य कार्यकर्ताओं द्वारा कार्रवाई
कान में घंटी की आवाज सुनाई देना, कम सुनाई देना, संतुलन ना रख पाना और बार बार गिरना	मुख्य रूप से स्ट्रेप्टोमायसिन, अमिकासिन, केनामायसिन, केप्रेओमाइसिन	**कान विषाक्तता** को दर्शाता है। तत्काल चिकित्सा अधिकारी से संपर्क करें और मरीज को चिकित्सा अधिकारी से जांच के लिए भेजें।
गतिविधियों की सुस्ती, चेहरे की सूजन, गर्दन में सूजन	मुख्य रूप से PAS और एथिओनामाइड	**थायराइड ग्रंथि का कार्य कम होना** दर्शाता है। तत्काल चिकित्सा अधिकारी से संपर्क करें और मरीज को चिकित्सा अधिकारी से जांज के लिए भेजें।
स्नायुओं और मांसपेशियों में दर्द एवं सूजन, चलने में असमर्थता	ओफ्लोक्सासिन, लिवोफ्लोक्सासिन, मोक्सीफ्लोक्सासिन	**स्नायु विकार** (Tendonitis) को दर्शाता है। तत्काल चिकित्सा अधिकारी से संपर्क करें और मरीज को चिकित्सा अधिकारी से जांच के लिए भेजें।
दौरा पड़ना: शरीर अकड़ना	आइसोनिआज़िड, सायक्लोसरीन ओफ्लोक्सासिन, लिवोफ्लोक्सासिन, मोक्सीफ्लोक्सासिन	तत्काल चिकित्सा अधिकारी से संपर्क करें और मरीज को चिकित्सा अधिकारी से जांच के लिए भेजें।
मूत्र, पसीना, कफ (बलगम), लार, आँसू में नारंगी या लाल रंग देखा जा सकता है। यह रंग रिफेम्पसिन लेने से आम तौर पे दिखाई देता है। अगर यह दिखे तो रोगियो को आश्वस्त करें।		

Prevention & Management of Adverse Reactions associated with Antitubercular Drugs

Ready Reckoner for Medical Officers / General Practitioners

Indian Council of Medical Research, Ministry of Health & Family Welfare, New Delhi

Central TB Division, Directorate General of Health Services, Ministry of Health & Family Welfare, Nirman Bhawan, New Delhi

2016

Side effects associated with anti-TB drugs and their prevention and management

Important general instructions:

1. Ensure that patient completes full course of anti-TB therapy
2. Side effects of anti-TB drugs can be an important cause of patient stopping medication, especially with second line drugs
3. Prevention and early detection of side effects are needed
4. Alcohol, smoking and use of illicit drugs increase side effects
5. Relevant history, clinical examination and lab tests are important to evaluate risk factors and diagnosis of side effects at an early stage
6. For contraception, ask patient to seek advice from family planning center as oral contraceptives are less effective with some anti-TB drugs
7. Educate, counsel and reassure patients for self-limiting side effects
8. For side effects and serious side effects, take immediate action and **refer patients to specialist** as suggested below
9. Report serious side effects to PvPI center (Procedure for reporting: Call your nearby PvPI center and provide complete information about side effect. Contact details of the nearest PvPI center are: Name of the Centre - _____; Contact no: _____; National toll free number: **1800 180 3024**)
10. Advice nutritious diet to TB patients
11. Advice patients about respiratory hygiene and provide information on preventing spread of TB (Cover nose and mouth with facemask, tissue paper)

ADRs with anti-TB drugs, their prevention and management:

ADRs	Diagnosis	Suspect Drug(s)	Differential Diagnosis / Other causes	Prevention	Management
Nausea and Vomiting	Clinical, based on complaints by patient	All oral anti-TB drugs	Hepatitis	Take anti- TB medication with banana	Symptomatic management. Exclude hepatitis / hepatoxicity
Rash, urticaria	Clinical	All anti-TB drugs	Steven Johnson syndrome, Anaphylactic reaction, Exfoliative dermatitis, Herpes infection	Seek past history of allergy before starting treatment and as applicable.	If rash involves <10%body surface area (BSA) and is not associated with mucous membrane involvement, treat with anti-histaminics. Stop suspect anti-TB drug and refer patient to specialist if indicated. Desensitization can be attempted. If it fails, substitute the suspect drug with alternate drug
Diarrhea	Clinical	All oral anti-TB drugs	Bacterial dysentery Amoebic dysentery, Malabsorption syndrome, Pseudomembranous colitis	Use of clean and potable water for drinking, washing hands before eating and drinking any thing	Advice Oral Rehydration Solution (ORS) 200 ml, after each loose stool. Check for infective causes.
Liver enzymes-SGOT / SGPT (AST / ALT) increased (up to 2xULN)	Increase of liver enzymes after starting anti-TB drugs	Frequent & Severe: PZA INH RIF Rare: EMB Ethionamide FQs PAS Cycloserine	Viral hepatitis – rule out by negative serological tests for A, B, C and E. Alcoholic hepatitis - AST:ALT > 2:1 with history of alcohol intake Amoebic liver abscess – Ultrasound / CT to detect cystic lesions / abscess	Up to 2xULN is not serious. Drug induced hepatitis is reported in 8-30% of patients. Avoid simultaneous administration of other hepatotoxic drugs. It can worsen to severe hepatitis, which can be prevented by monitoring	Usually drugs are not withdrawn. Check for other potential hepatotoxic agents e.g. alcohol

ADRs	Diagnosis	Suspect Drug(s)	Differential Diagnosis / Other causes	Prevention	Management
			Mass in ultrasound/CT→ Liver biopsy to rule out Hepatoma	of LFT in high risk patients every 15 days & taking appropriate action if liver enzymes increase.	
Hepatitis (Severe)	ALT / AST >3×ULN with symptoms of Nausea, vomiting, anorexia, jaundice, dark colored urine OR ALT/ AST >5×ULN without symptoms	<u>Frequent & Severe:</u> PZA INH RIF <u>Rare:</u> Ethionamide PAS Cycloserine Clarithromycin Clofazimine Imipenem-cilastatin	Investigate as above to rule out: Viral hepatitis Alcoholic hepatitis - Amoebic liver abscess Hepatoma	Early detection of raised liver enzymes to prevent worsening & reduce associated morbidity & mortality	Management includes withdrawal of potential causative drugs & supportive treatment. Later, when enzyme levels return to normal, then gradually reintroduce the drugs. (Refer to flowcharts)
Exfoliative and allergic dermatitis	Clinical based on symptoms - Pruritus, widespread erythema and epidermal sloughing	<u>Frequent:</u> FQs <u>Rare:</u> RIF PAS Cycloserine linezolid Amoxicillin-clavulanate clarithromycin Clofazimine	Asteatotic Eczema Contact Dermatitis, Drug-Induced Bullous Disorders Drug-Induced Photosensitivity Nummular Dermatitis Perioral Dermatitis Phytophotodermatitis	Early detection and management can prevent worsening	Topical hydrocortisone or oral antihistamines may be helpful to control pruritus. Anti-TB medications should not be discontinued unless an equally effective drug is available for substitution. Refer to specialist if indicated.
Stevens-Johnson and Toxic epidermal necrosis	Clinical based on total body surface area (BSA) involvement of more than 10%	<u>Rare:</u> INH RIF EMB FQs	Staphylococcal scalded skin syndrome Irradiation – History of radiation Trauma - History	Early detection and management can prevent worsening	Immediate drug withdrawal and referral to specialist is recommended. Reintroduction is not recommended. Supportive therapy like antihistamines,

ADRs	Diagnosis	Suspect Drug(s)	Differential Diagnosis / Other causes	Prevention	Management
	and / or mucous membrane involvement	Amoxicillin-clavulanate clarithromycin imipenem-cilastatin	Progressive systemic sclerosis (scleroderma) – ANCA antibodies		anti-inflammatory agents may be helpful in the meantime.
Psychosis (Severe)	Symptoms of Hallucinations, paranoia, suicidal or abnormal thoughts or actions	<u>Frequent & Severe:</u> Cycloserine <u>Frequent:</u> INH <u>Rare:</u> RIF, FQs Clarithromycin Clofazimine Imipenem-cilastatin	Post-traumatic Stress Disorder, Delusional disorder, Schizophrenia, Schizophreniform Disorder	Careful monitoring. Psychiatric counseling at the start of treatment in patients at risk of psychiatric disorders.	Refer to specialist for further evaluation. Consider suspect drug withdrawal. Refer to specialist.
Peripheral neuropathy	Clinical symptoms of Burning and paresthesia in extremities. Electromyography (nerve conduction studies) for confirmation	<u>Frequent:</u> INH <u>Rare:</u> EMB FQs PAS Ethionamide Cycloserine Linezolid (Severe)	Neuropathy due to high dose of pyridoxine Diabetic neuropathy Peripheral demyelinating disease	Supplementing the anti-TB drugs with Pyridoxine 5-10 mg orally once a day while patient is on INH Pyridoxine 50 mg per day with Linezolid and with every 250 mg Cycloserine	Check for Pyridoxine compliance Give paracetamol / NSAIDs to alleviate pain. Drug withdrawal is not indicated. Start Pyridoxine 100 mg per day. If no response, increase dose of Pyridoxine to 200 mg. Refer to specialist if no response or if patient is taking Linezolid.
Ototoxicity/ Hearing loss/ Deafness	Symptoms- Tinnitus, vertigo, Loss of balance and equilibrium. Audiometry for confirmation	<u>Frequent & Severe:</u> AGs <u>Rare:</u> Linezolid clarithromycin imipenem-cilastatin	Ear wax, otitis media, Traumatic hearing loss, Meniere's disease Acoustic neuroma	Monitoring of early symptoms can prevent permanent ear damage	Consider withdrawal of the suspect drug. Refer to specialist for further evaluation

ADRs	Diagnosis	Suspect Drug(s)	Differential Diagnosis / Other causes	Prevention	Management
Optic neuritis	Vision loss, Peri-ocular pain, Dyschromatopsia (disorder of color vision), based on symptoms and ophthalmic examination for confirmation	Frequent & Severe: EMB Rare: PAS Ethionamide Clofazimine Linezolid (Severe)	Brain Tumor, Giant cell arteritis, Retinal detachment, Multiple sclerosis, Closed-angle glaucoma, Cataract, Macular degeneration, Diabetic retinopathy	Regular ophthalmologic examination	Consider withdrawal of the suspect drug. Refer to specialist for further evaluation
Immune Nephrotoxicity	Serum creatinine >2×baseline. Presence of Auto-antibodies in the blood is confirmatory	RIF, especially when restarted after stopping for few weeks	Urinary tract infection, Post streptococcal glomerulonephritis, Minimal change disease, Rapidly progressing glomerulonephritis	Patients should be counseled not to stop and restart rifampicin randomly, on their own	Consider drug withdrawal and refer to specialist.
Flu Syndrome	By symptoms- Chills, malaise, dry cough, shortness of breath, loss of appetite, body aches and nausea	Frequent: RIF - Specially with alternate day regimen	Viral infections: Influenza, Dengue Fever: Dengue NS1 antigen test positive	Patients on daily regimen have reported lower frequency and less severe flu as compared to the patients on intermittent regimen	Oral antihistaminics and paracetamol, according to the symptoms
Arthralgia / Arthritis	Joint pain, swelling involving one or more joint. High uric acid levels, demonstration of tophi crystals in joint is confirmatory of Gout	Frequent & Severe: PZA Rare: EMB INH	Osteoarthritis, Rheumatoid arthritis	Early diagnosis and management can prevent progression and can improve quality of life	Therapy with paracetamol / NSAIDs can be used for pain relief as needed / Colchicine can be given in gout.
Thrombocytopenia	Blood platelet count <50000 / mm^3 indicates thrombocytopenia, Drug induced	Frequent & Severe: RIF FQs	Dengue hemorrhagic fever – Dengue NS1 antigen test positive Malaria – Peripheral blood smear, malaria antigen test	Patients should be advised not to skip the doses of anti-TB drugs as the incidence of drug-induced	Manage with platelet transfusion and consider withdrawal of suspect drug. It is important to remember that

ADRs	Diagnosis	Suspect Drug(s)	Differential Diagnosis / Other causes	Prevention	Management
	thrombocytopenia is diagnosed by excluding other causes of thrombocytopenia	Rare: INH EMB PZA AGs PAS Ethionamide Cycloserine Amoxicillin-clavulanate Clarithromycin Imipenem-cilastatin Linezolid	Liver Cirrhosis – Liver Biospy Thrombotic Thrombocytopenic Purpura – Blood picture showing thrombocytopenia and hemolytic anemia with clinical symptoms Acute Leukemia – Bone marrow examination	thrombocytopenia has been reported to be higher when the drug is not taken continuously Regular monitoring of platelet levels can facilitate early detection & thus, reduce the associated morbidity & mortality	anti-TB drugs can cause thrombocytopenia.
Leucopenia	Leucocyte count less than 2000/mm^3 Neutropenia: Absolute neutrophil count less than 1000/mm^3 Routine blood counts	Rare: INH EMB RIF FQs AGs Ethionamide Linezolid Amoxicillin-Clavulanate Clarithromycin Imipenem-cilastatin	Typhoid, malaria, dengue, Rickettsial infections, HIV, thyroid disorders, aplastic anemia, rheumatoid arthritis, vitamin B12 or folate deficiency, mineral deficiencies of copper and zinc. Bone marrow diseases: Myelodysplastic syndrome, leukemia, Autoimmune disorders: SLE, Bone marrow damage or suppression Drug induced Leucopenia: Clozapine, Valproate, Lamotrigine, Interferons and Bupropion	Monitoring of the complete blood count as indicated, will help in early identification. Avoid simultaneous administration of other drugs that can cause leucopenia.	If the total leucocyte count is <2000/ mm^3 or absolute neutrophil count < 1000/mm^3. **Refer the patient to specialist as this is serious.**
Nephrotoxicity	Serum creatinine more the twice the baseline with	Frequent & Severe: **AGs**	Chronic renal failure, Alcoholic ketoacidosis, Diabetic ketoacidosis,	Dose adjustment in patients with pre-existing renal disease,	Dose adjustment in patients with pre-existing renal disease. In cases of lack of response

ADRs	Diagnosis	Suspect Drug(s)	Differential Diagnosis / Other causes	Prevention	Management
	symptoms of Oliguria, Loss of appetite, General ill feeling and fatigue	Rare: Linezolid	Metabolic acidosis, Urinary tract infection	monitoring of renal function as indicated	consider drug withdrawal and refer to specialist.
Hyperglycemia	Fasting blood sugar more than 160 mg/dl with polydypsia, polyphagia, polyuria.	Rare: RIF INH FQs Moxifloxacin Clofazimine	Uncontrolled diabetes mellitus, Impaired glucose tolerance	Regular Blood sugar monitoring in high risk patients can help in early detection.	Individualized diet, exercise, patient education and glucose-lowering therapies.
Hypoglycemia	Blood sugar less than 55 mg/dl with weakness, palpitation, loss of consciousness, seizures.	Rare: INH Ethionamide Clarithromycin	Prolonged starvation, Overdose of insulin or oral hypoglycemic agents in diabetic patients	Regular Blood sugar monitoring in high risk patients for early detection	In case of severe hypoglycemia, withhold all hypoglycemic medications. Glucose to be given orally or I.V. as appropriate.
Hypothyroidism	TSH level >10 mIU/L with tiredness, increased sensitivity to cold, weight gain, constipation, depression, lethargy	Rare: PAS Ethionamide Cycloserine	Hypothyroid Goitre - TSH levels high Myxoedema - Hashimotos thyroiditis – Anti-thyroid antibodies Riedels thyroiditis - Antibodies	Early diagnosis, followed by prompt treatment can help to prevent worsening.	All patients with TSH >10 mIU/L, whether symptomatic or not, should be started on Levothyroxine
Pseudomembranous colitis	Watery diarrhoea with or without blood, associated with stomach cramps and high fever, stool examination	Frequent & Severe: Amoxicillin-clavulanate Clarithromycin Imipenem-cilastatin Linezolid	Viral diarrhea, Bacterial diarrhea, Amoebic dysentery, Malabsorption syndrome - Chronic condition accompanied with weight loss	Judicious use of antibiotics, use of probiotics	Vancomycin and metronidazole are effective. Refer to specialist. Consider withdrawal of the suspect drug.

ADRs	Diagnosis	Suspect Drug(s)	Differential Diagnosis / Other causes	Prevention	Management
		Rare: RIF FQs			
Gynaecomastia	Clinical symptoms and biopsy	Rare: INH RIF Ethionamide	Lipomas, dermoid cysts, sebaceous cysts, ductal ectasia, hematomas, and fat necrosis FNAC will provide diagnosis	Resolves after stopping anti-TB drugs	Reassure patient and in severe cases, withdraw suspect drug.
Pellagra-like syndrome	Based on clinical symptoms of Dementia, Dermatitis and Diarrhea	Rare: INH Ethionamide	Chronic alcoholism – Malnutrition Amino acid imbalance - Hypoalbuminemia	Supplementation with nicotinamide and pyridoxine	Check for compliance. Increase the dose of nicotinamide and pyridoxine if required.
QT prolongation Torsade de pointes Arrhythmia	QTc ≥ 501 ms on at least two separate ECGs and /or arrhythmia on ECG	Rare: FQs Moxifloxacin Clofazimine Linezolid Clarithromycin	Hypokalemia, Metabolic acidosis, Atrial fibrillation, atrial flutter, ventricular arrhythmia, Paroxysmal supraventricular tachycardia	ECG of patients on FQs as and when indicated	Refer to specialist for management

Pancreatitis, Peptic ulcer, Depression, Encephalopathy, Pneumonitis, Myopathy, Rhabdomyolysis, Congestive cardiac failure, Pericarditis have also been reported **rarely** with anti-TB drugs.

Peripheral neuropathy, anemia, thrombocytopenia and optic neuritis with Linezolid (2nd line drugs) can be severe and need immediate referral to specialist.

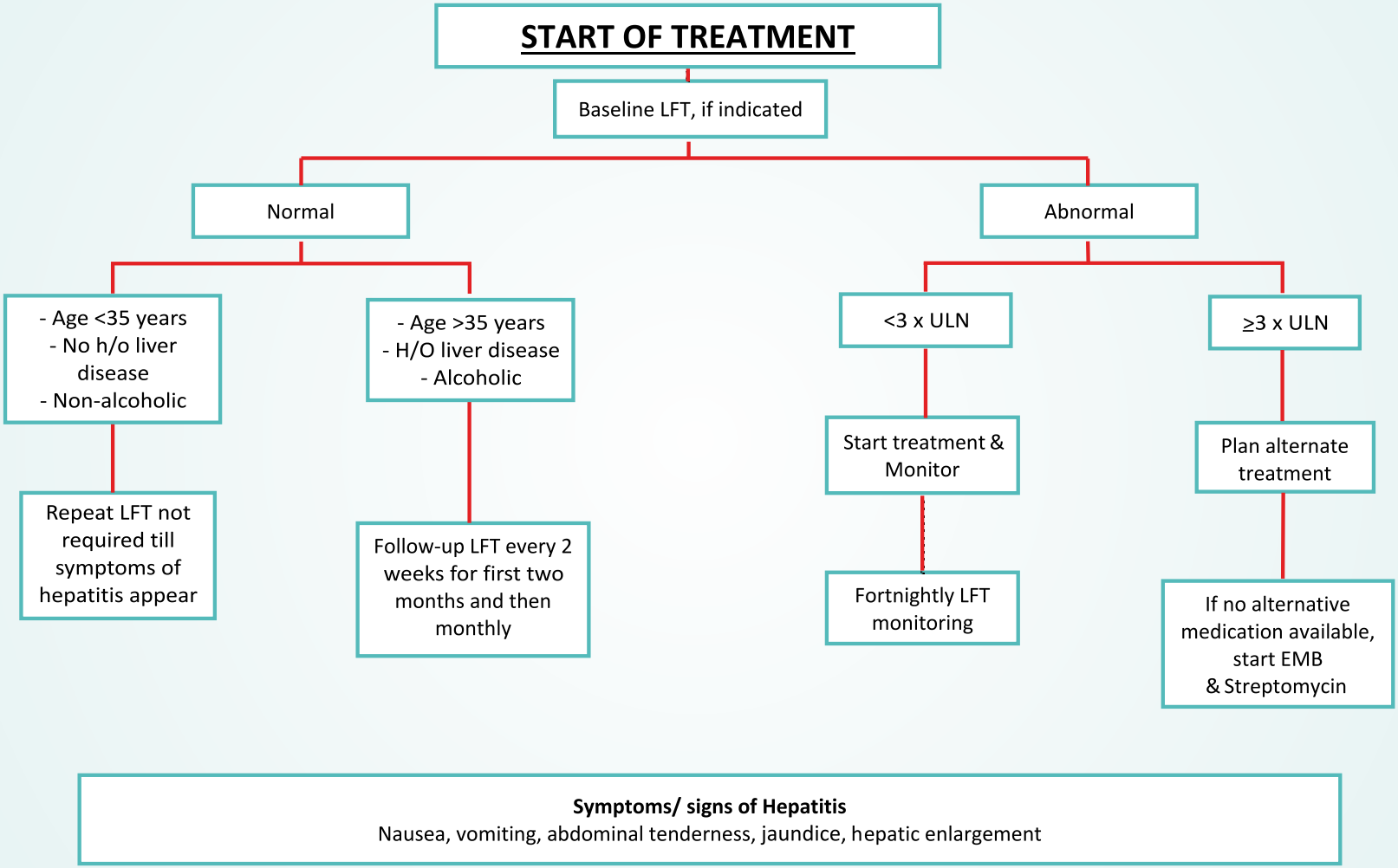
Frequent: Seen in 1-10% patients
Rare: Seen in less than 1% patients

Laboratory tests for TB patients:

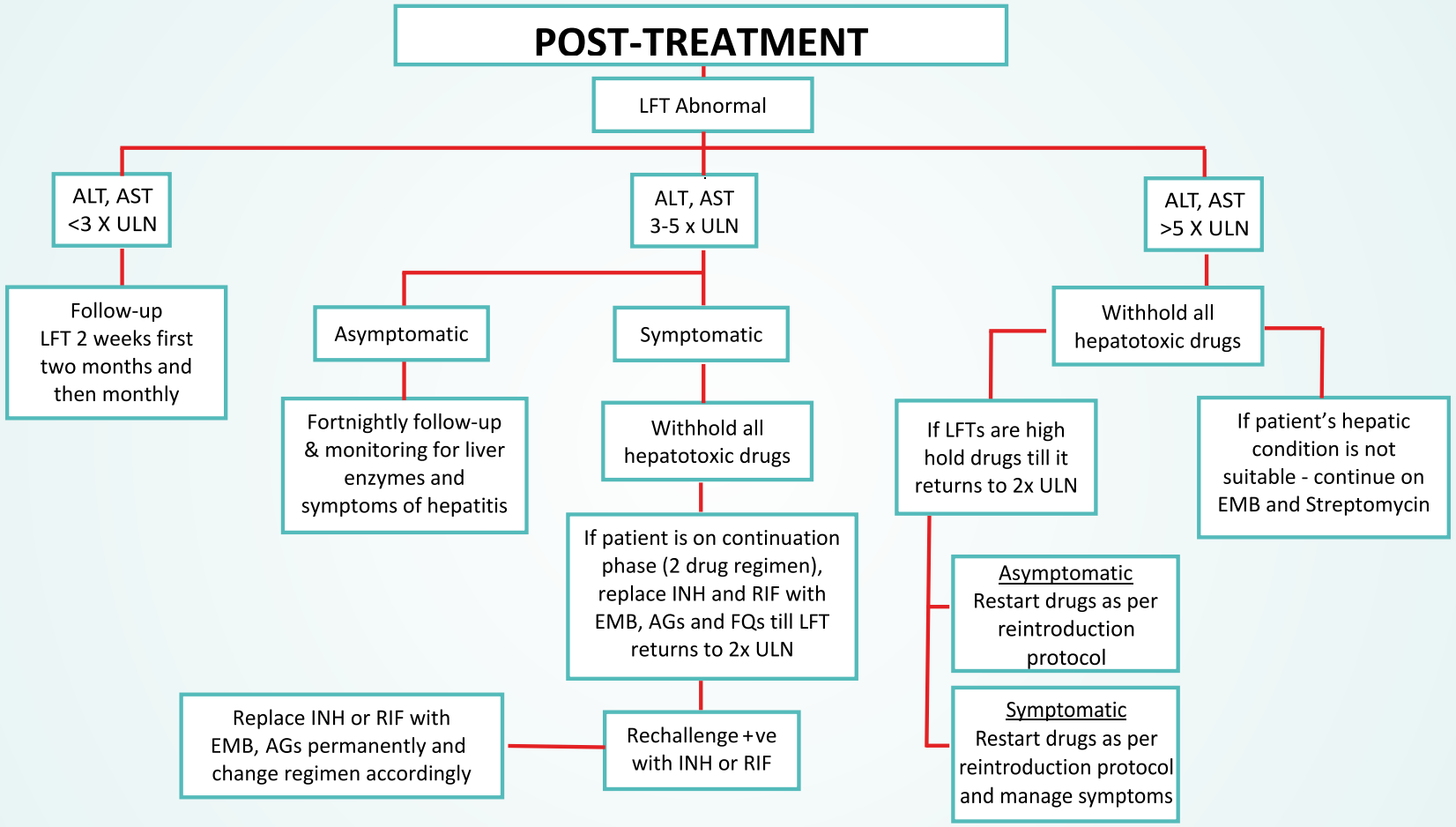
Timepoints	Laboratory tests
Baseline (Before initiating treatment if indicated)	1. LFT (ALT, AST, Serum bilirubin) 2. RFT (Serum creatinine, Blood Urea, Urine routine and microscopy) 3. Complete blood count, peripheral smear and Hb 4. Blood glucose: Fasting and post-prandial (Random in non-diabetics) 5. Total serum proteins, Albumin and Globulin 6. Serum uric acid 7. Serum electrolytes 8. Thyroid function tests (T3, T4 and TSH) 9. Ophthalmologic examination 10. Psychiatric consultation (before starting Cycloserine) 11. In females: Urine pregnancy test and USG of abdomen and pelvis
After 1.5 months	Ophthalmologic examination (for patients taking Ethambutol), if indicated
After 2 months of treatment as indicated	Tests mentioned at the baseline will be repeated. Ophthalmologic examination: If EMB is stopped at or before 2 months, not required. If EMB is continued and ophthalmologic examination was not performed at 1.5 months, then it should be done.

Tests to be performed at 2 months will be repeated at 4 and 6 months if indicated.

Appendix 4 — **Hepatotoxicity with AKT and management**



Appendix 4 — Hepatotoxicity with AKT and management



Reintroduction protocol

After resolution of symptoms and LFT returns to ≤2 x ULN, reintroduce one drug at a time. Start with INH; if patient is asymptomatic for 3 days, add RIF. If patient is asymptomatic for next 3 days, add next drug and so on. If symptoms recur, replace the responsible drug.
Do not reintroduce PZA as much as possible.

Warning symptoms for some serious adverse reactions:

Warning Symptoms	For Medical officer / General practitioner (GP): When to refer the patient
Rash Skin lesions on oral cavity, nose	If mucous membranes are involved OR rash is more than 10% of body surface area without mucous membrane involvement OR associated with fever and generalized swelling (edema); **refer to specialist / tertiary care center immediately.**
Pain in eye/s, Blurring of vision and Disturbance in color vision	Indicates **Eye toxicity** **Refer the patient to specialist for evaluation.**
Loss of hearing / Diminished hearing, Ringing in the ears, Dizziness and Loss of balance	Indicates **Ear toxicity** **Refer the patient to specialist** for evaluation.
Puffiness of face, Swelling over feet and Oliguria, Anuria	Indicates **Kidney toxicity** Treat the symptoms and **refer the patient to specialist for evaluation.**
Hallucinations, Seeing abnormal things and Suicidal or abnormal thoughts or actions	Indicates **Psychiatric disturbances**. **Refer the patient to specialist** for evaluation.

Absolute contraindications of anti-TB drugs : (Benefit - Risk have to be carefully assessed)

Drug	Absolute contraindications	Reason
Rifampicin	With Saquinavir and Ritonavir	Potential for hepatotoxicity is increased. Rifampicin is CYP3A4 inducer and can decrease Saquinavir level and effect
Ethambutol	Optic neuritis	Ethambutol can cause optic neuritis
Pyrazinamide	Acute porphyria Gouty arthritis Hepatic diseases	Pyrazinamide can precipitate acute porphyria Can inhibit excretion of urates Can cause drug induced hepatitis
Neomycin Kanamycin, Tobramycin, Amikacin, Capreomycin, Streptomycin	Concurrent use of two aminoglycosides With potent diuretics e.g. Furosemide Soon after use of anesthetics and muscle relaxants	Can potentiate nephrotoxicity Can potentiate ototoxicity Can result in respiratory paralysis
Levofloxacin, Ofloxacin, Moxifloxacin	History of tendon disorders	Associated with risk of tendinitis and tendon rupture
Ethionamide	Severe hepatic impairment	Risk of worsening
Cycloserine	Epilepsy, Psychiatric illness - Depression, Severe anxiety, Psychosis Severe renal insufficiency	Can precipitate seizures Can lead to severe psychosis and depression Can lead to Cycloserine toxicity
Clarithromycin	With Pimozide, Astemizole With Lovastatin or Simvastatin Hypokalemia and in patients with prolonged QT interval	Risk of QT prolongation Can cause rhabdomyolysis Risk of further QT prolongation
Imipenem	With Valproic acid and Probenecid	Decrease in valproic acid concentration and Increase in plasma levels of imipenem
Linezolid	With Monoamine oxidases A or B inhibitors (e.g. phenelzine, isocarboxazid, selegiline, moclobemide) within two weeks	Risk of MAO inhibition leading to serotonin syndrome

Algorithm for reintroduction of anti-TB drugs - To be done by experts only:

Adverse drug reaction	Advice on reintroduction
Hepatotoxicity	Reintroduction after liver enzyme returns to ≤ 2 X ULN
Ocular toxicity	Main suspect drug is EMB Reintroduction of Ethambutol is not recommended
Immune mediated Nephritis	Main suspect drug is RIF Reintroduction with RIF is not recommended
Non serious cutaneous ADRs - no mucous membrane involvement or less than 10 % of BSA.	After withholding all drugs reintroduce one drug at a time
Serious Cutaneous adverse drug reactions - mucous membrane involvement or more than 10 % of BSA.	Reintroduction is not recommended (applies for all anti-TB drugs).
Immune thrombocytopenia	Main suspect drug is RIF Reintroduction with RIF is not recommended
Gynecomastia	Symptoms takes long time to resolve (4-12 month) hence usually reintroduction is not required.
Aplastic Anemia	Main suspect drug is INH Reintroduction with INH is not recommended
Nephrotoxicity	Main suspect drugs are AGs. AGs can be reintroduced at low doses after the renal function returns to normal.
Ototoxicity	Main suspect drugs are AGs. Reintroduction of AGs is not recommended.
Cardiac arrhythmias including Torse de pointes (TdP)	Main suspect drugs are FQs. Reintroduction with FQs is not recommended.
Diarrhea	Reintroduction is recommended with one drug at a time every fourth day, once diarrhea is resolved
Seizures	Main suspect drugs are FQs. Reintroduction with FQs is not recommended.
Psychosis	Main suspect drugs is cycloserine. Reintroduction with cycloserine can be done at low dose but if symptoms recur than completely discontinue the drug.

Stepwise increase in the dosage for Reintroduction

1. Reintroduction of anti-TB drugs:

Drug	Day 1	Day 2	Day 3
Isoniazid	50 mg	Full dose	Full dose
Rifampicin	75 mg	300 mg	Full dose
Pyrazinamide	250 mg	1000 mg	Full dose
Ethionamide / Prothionamide	125 mg	250 mg	Full dose
Fluoroquinolones	50 mg	200 – 250 mg	Full dose
Cyclosporine	125 mg	250 mg	Full dose
Ethambutol	100 mg	500 mg	Full dose
PAS	1 g	4 g	Full dose
Capreomycin	125 mg	500 mg	Full dose
Kanamycin	125 mg	500 mg	Full dose
Amikacin	125 mg	500 mg	Full dose

If the test dose of any drug causes a reaction, discontinue this drug, unless it is deemed essential to the regimen. If that is the case, desensitization can be considered.

2. Reintroduction of the drugs should be in hospitalized patients.

3. In patients with severe rash, dose increment should be slower than stated above.

4. For key drugs, Isoniazid, Rifampicin, Ethambutol, detailed desensitization protocol with very small dose and method of dosage preparation is available on the website (http://www.who.int/topics/tuberculosis/en/)

Anti-TB drugs in pregnant & lactating women:

Pregnancy:

- All female patients in reproductive age-group should be tested for pregnancy during initial evaluation
- Generally pregnancy should be avoided in TB patients
- Aminoglycosides (streptomycin, kanamycin, amikacin) are contraindicated throughout pregnancy
- Ethionamide is contraindicated in first trimester of pregnancy
- Mother's malnutrition may affect the development of the fetus
- Continuation of pregnancy should be done in consultation with gynecologist / obstetrician
- Pregnant patients need to be monitored carefully both in relation to treatment and progress of the pregnancy

Lactation:

Breast feeding should not be discouraged. The mother should be advised about cough hygiene measures such as covering the nose and mouth while breast feeding, coughing, sneezing or any act which can produce sputum droplets. Most of the anti-TB drugs cross into breast milk at low levels. However the doses of drugs that babies receive via **breast milk are insufficient to treat or prevent TB in the infant**. Mothers receiving INH and their breastfed infants should be supplemented with vitamin B6 (pyridoxine), **recommended dose of Pyridoxine in infants is 5 mg/day**.

Contraception:

Rifampicin decreases the efficacy of oral contraceptives by increasing their metabolism so the use of Oral Contraceptive Pill (OCP) is not recommended during TB treatment. As per the patient's choice and availability, one of the following methods are recommended:

1. Double barrier method of contraception i.e. condom with spermicide (foam, gel, cream, or suppository), diaphragm (including occlusive cap or cervical/vault) with spermicide
2. IUD
3. Medroxyprogesterone acetate
4. High dose estrogen OCP

Anti-TB drugs in renally impaired patients:

Dose modification for anti-TB drugs: Severity of renal impairment is defined by creatinine clearance (CrCl) and renal impairment is considered as: mild (1.5-2 mg/dL serum creatinine) moderate (2-3 mg/dL serum creatinine) and severe (> 3 mg/dL serum creatinine).

Estimated creatinine clearance calculations: Men: Weight (kg) X (140 – age) / 72 X serum creatinine (mg/dl)

Women: 0.85 X Weight (kg) X (140 – age) / 72 X serum creatinine (mg/dl))

Drug	Recommended dose and frequency for patients with CrCl < 30 ml/min or for patients receiving haemodialysis	Drug	Recommended dose and frequency for patients with CrCl < 30 ml/min or for patients receiving haemodialysis
Isoniazid	No adjustment necessary	Gatifloxacin	400 mg three times a week
Rifampicin	No adjustment necessary	Cycloserine	250 mg once daily, or 500 mg / dose three times per week
Pyrazinamide	25-35 mg/kg per dose three times per week (not daily)	Prothionamide	No adjustment necessary
Ethambutol	15-25 mg/kg per dose three times per week (not daily)	Ethionamide	No adjustment necessary
Streptomycin	12-15 mg/kg per dose two or three times per week (not daily)	PAS	4 g/dose, twice daily maximum dose
Capreomycin	12-15 mg/kg per dose two or three times per week (not daily)	Linezolid	No adjustment necessary
Kanamycin	12-15 mg/kg per dose two or three times per week (not daily)	Clofazimine	No adjustment necessary
Amikacin	12-15 mg/kg per dose two or three times per week (not daily)	Amoxicillin/ clavulanate	For 10-30 ml/min dose 1000 mg as amoxicillin component BD; For CrCl <10 ml/min dose 1000 mg as amoxicillin component OD
Ofloxacin	600-800 mg per dose three times per week (not daily)	Imipenem / cilastin	For CrCl 20-40 ml/min dose 500 mg every 8 hours; For CrCl <20 ml/min dose 500 mg every 12 hr
Levofloxacin	750-1000 mg per dose three times per week (not daily)	Meropenem	For CrCl 20-40 ml/min dose 750 mg every 12 hr For CrCl <20 ml/min dose 500 mg every 12 hr
Moxifloxacin	No adjustment necessary	High dose isoniazid	Recommendations not available

Commonly used ancillary medicines:

Management of adverse reaction often requires use of ancillary medicines to reduce or lessen side effects. Below is list of indications and commonly used medicines for management of adverse reactions.

Indication	Drugs
Nausea, vomiting, Stomach upset	Domeperidone, metoclopramide, prochlorperazine, promethazine, ondansetron
Heartburn, indigestion and acidity	H2-blockers (ranitidine etc.), proton pump inhibitors (omeprazole, pantoprazole etc) Antacid syrups and the antacids if prescribed should be taken at least 2 hours apart from anti-TB drugs
Oral candidiasis	Fluconazole, clotrimazole lozenges, nystatin suspension
Diarrhoea	ORS sachets
Prophylaxis of peripheral neuropathy of cycloserine and isoniazid	Pyridoxine (vitamin B6)
Musculoskeletal pain, **Arthralgia, headaches**	Give paracetamol / ibuprofen / aspirin / diclofenac. If caused by fluoroquinolones, refer to specialist immediately. Tendonitis can progress to tendon rupture.
Cutaneous reactions, itching	Hydrocortisone cream, calamine lotion
Systemic hypersensitivity **Reactions**	Antihistamines (diphenhydramine, chlorpheniramine, dimenhydrinate) Systemic corticosteroids (prednisone, prednisolone, Dexamethasone) are reserved only for very severe reactions
Bronchospasm	Inhaled beta-agonists (salbutamol, albuterol, etc.), inhaled corticosteroids (beclomethasone, etc.)
Hypothyroidism	Levothyroxine
Electrolyte wasting	Potassium and magnesium replacement therapy (oral formulations)

Prevention & Management of Adverse Reactions associated with Antitubercular Drugs

Reference Manual for Medical Officers / General Practitioners

Indian Council of Medical Research, Ministry of Health & Family Welfare, New Delhi

Central TB Division, Directorate General of Health Services, Ministry of Health & Family Welfare, Nirman Bhawan, New Delhi

2016

Contents

This Reference Manual will be made available on website of Indian Council of Medical Research (http://www.icmr.nic.in/) and Central TB Division (http://www.tbcindia.nic.in/)

Prevention & Management of Adverse Reactions associated with Antitubercular Drugs

Reference Manual for Specialists

Indian Council of Medical Research, Ministry of Health & Family Welfare, New Delhi

Central TB Division, Directorate General of Health Services, Ministry of Health & Family Welfare, Nirman Bhawan, New Delhi

2016

Contents

Contents

This Reference Manual will be made available on website of Indian Council of Medical Research (http://www.icmr.nic.in/) and Central TB Division (http://www.tbcindia.nic.in/)