Chapter - TWO

Review of Literature
2.1 TUBERCULOSIS

Referred to in the Vedas and Ayurvedic Samhitas. Pharaoh some 4,000 years ago in ancient Egypt, described about the disease, become one of the largest single causes of death: a disease that would later be called tuberculosis. In 460 the great thinker Hippocrates speculated that the coughing in many of his patients are related to air they breathed. He suggested that persons afflicted with TB take long rides on horseback because; the fresh air would help the patients to breathe easier (WHO, 2004).

Celsius (1742) later confirmed TB of the lungs as a separate disease. He also made the connection between the air people breathed and TB, and recommended that TB patients should spend their days at sea and drink lots of milk. In 1882 Robert Koch under the microscope, saw for the first time in history the organism that had taken so many lives, what an English doctor, Benjamin Marten, had once called "wonderfully minute living creatures". Koch used a special staining method to see "tubercle bacillus" (WHO, 2004; Kumar, 2005).

X-ray discovered in 1895 by Wilhelm Conrad Roentgen, a tool which made an important milestone in the understanding of the disease. This helped Roentgen to examine the lungs of living persons for signs of tubercular lesions. Over the next century, the development of other means such as skin test and sputum microscopy, helped refine diagnosis methods (WHO, 2004). Robert Koch’s discovery of the tubercle bacillus in 1882 (Koch, 1938) proved that TB was an infectious disease. As diagnostic methods began to improve, prevention and treatment becomes easier. In 1921, two French scientists, Calmette and Guerin, invented a vaccine that is now known as BCG (Bacille Calmette-Guer). As a preventive measure, it was extensively used in most of the European countries in 1920s (Keers, 1978). They hoped that this vaccine would prevent people from developing the disease. However, even now, after decades of research, BCG remains of only limited use in halting the spread of TB - it can prevent against severe forms of TB, but has virtually no impact on the spread of the most common form, active pulmonary TB (Keers, 1978).

Then, in 1944, scientists developed a medicine that eventually replaced sanatoriums as the leading treatment and that has saved thousands of lives. In that year, an antibiotic, or a medicine to kill bacteria, was used on a patient with impressive results. The coughing and fever, the same symptoms that had plagued the ancient Egyptian, stopped.
patient recovered and for the first time, the bacterium had met its match. The first effective medication for TB, streptomycin (1944), was discovered, rapidly followed by para-aminosalicylic acid (PAS) and later isoniazid (1952), pyrazinamide (1954), ethambutol (1962) and the rifamycins in 1969 (Ryan, 1992).

In the 1990s, the World Health Organization established a new strategy for treating patients, called Directly Observed Treatment, Short-course (DOTS).

The rapid rise in incidence of TB globally led the World Health Organization to declare the disease a global emergency (WHO, 1998). It is estimated that one in three of the world's population is infected, resulting in millions of cases of active, infectious disease and some 3 million deaths per annum - a figure predicted to rise (Kochi, 1991). The highest TB rates of 4300 cases/100,000 of the population are generally found in the countries of sub-Saharan Africa. However, huge areas of the world, including the Indian Subcontinent, Far East, China and the former Soviet Union, have rates between 100 and 300 cases/100,000.

In 2006 nearly 9.2 million new cases and 1.7 million deaths were reported due to TB worldwide and over 90% of these occurred in the low and middle income countries (WHO, 2008). Tuberculosis (TB) is a major public health problem in India. India is the highest TB burden country accounting for one fifth of the global incidence (Global annual incidence estimate is 9.1 million cases out of which it is estimated that 1.9 million cases are from India). India is 17th among 22 High Burden Countries in terms of TB incidence rate (WHO, 2009). Each year nearly 2 million people in India develop TB, of which around 0.87 million are infectious cases. It is estimated that annually around 330,000 Indians die due to TB.

2.2 TYPES OF TUBERCULOSIS

Tuberculosis may occur in any part of the body. On the basis of site of tuberculosis it is mainly divided into two categories: pulmonary and extra-pulmonary. Both pulmonary and extra-pulmonary TB is further divided into 5 and 7 different category respectively which is described in details in Table 1.
<table>
<thead>
<tr>
<th>Table 1: Type of tuberculosis based on site of occurrence</th>
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<tbody>
<tr>
<td><strong>Pulmonary tuberculosis</strong></td>
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<tr>
<td><strong>Laryngeal TB:</strong> Laryngeal tuberculosis is very rare and accounts for less than 1% of all TB cases (Alvarez and McCabe, 1984). It affects the throat, in the vocal chord area. An indirect laryngoscopic examination showed irregularity of right vocal cord. Two types of lesions are produced and recognized clinically i.e., exudative and productive types. It is highly contagious and misdiagnosis can pose a serious risk to the public health. (Brown et al., 1965; Bailey and Taylor, 1981).</td>
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<tr>
<td><strong>Cavitary TB:</strong> In Cavitary TB, bacteria cause progressive lung (mainly upper lobes) destruction by forming cavities, or enlarged air spaces because they are highly oxygenated. The pathogenic evolution of these lesions is not fully understood. It is highly contagious and patients with cavitary lung lesions are the main source of disease transmission, whereas patients with smear negative disease can also infect others. (Behr et al., 1999; Iseman, 2000; Nardell and Piessens, 2000). Cavitary disease on chest radiography is associated with increased time before sputum smears and cultures convert to negative following initiation of antituberculous chemotherapy more likely that will harbor drug-resistant organisms (Telzak et al., 1997).</td>
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</table>
Miliary TB (Disseminated TB): Miliary tuberculosis (TB) refers to clinical disease resulting from the uncontrolled hematogenous dissemination of *M. tuberculosis* and describes the appearance in chest X-ray of very small nodules throughout the lungs that look like millet seeds (Sharma *et al.*, 2005). The clinical presentation of miliary tuberculosis is highly variable. When it develops during primary infection, the disease has a more acute onset and more rapid clinical course. The patient becomes acutely ill with high fever and is in danger of dying. Acute disease may be fulminant, including multiorgan system failure (Sydow *et al.*, 1992), a syndrome of septic shock (Ahuja *et al.*, 1992), and acute respiratory distress syndrome (ARDS) (Piqueras *et al.*, 1987; Mohan *et al.*, 1996).

**TB Pleurisy:** Tuberculous (TB) pleurisy can cause clinical symptoms and pleural fibrosis with resultant residual pleural thickening (RPT) (Light, 2001). Pleural TB involvement may increase the vascular permeability of the pleura, leading to pleural fluid accumulation. This pleural fluid is enriched in proteins, inflammatory cells, and various proinflammatory and profibrotic cytokines (Antony, 2003). Delayed diagnosis and/or treatment of TB pleurisy may cause disordered fibrin turnover in the pleural cavity with subsequent fibrin deposition and loculation of pleural fluid, and may impair uneventful resolution of pleural effusion (Chung *et al.*, 2005).
**Extra pulmonary TB**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
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<tr>
<td>Adrenal Tuberculosis</td>
<td>Patients suffering from this form of TB are known to experience fainting or weakness. Active adrenal tuberculosis always wrong diagnosed as adrenal insufficiency or addison's disease. This can be diagnosed by computed tomography which shows hypertrophy of the adrenal gland, which may be bilateral or unilateral. During antituberculosis chemotherapy a progressive change of the adrenals toward atrophy and calcification, while the adrenal function remained impaired. Computed tomography seems to be useful in the aetiological diagnosis of Addison's disease (Taki et al., 2008).</td>
</tr>
<tr>
<td>Lymph node disease</td>
<td>It is characterized by the patients experience enlargement of the lymph nodes. The nodes could also rupture through the skin.</td>
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<tr>
<td>Osteal Tuberculosis</td>
<td>This form of TB affects the bones. The affected area's bone tissue weakens, and it could cause the patient to fracture the affected area.</td>
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<tr>
<td>TB Peritonitis</td>
<td>It usually affects the outer lining of the intestine. Due to the TB, fluid gets collected in the outer lining of the intestine, causing the affected to experience pain in the abdomen.</td>
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<tr>
<td>Renal TB</td>
<td>It is characterized by the patient experiencing pyuria, which is the presence of white blood cells in the urine. It could end up affecting the reproductive organs and cause Epididymitis in men.</td>
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<tr>
<td>TB Meningitis</td>
<td>The symptoms for this include the patients displaying signs of being affected by a stroke or a brain tumor. It is extremely dangerous and could even prove to be fatal.</td>
</tr>
<tr>
<td>TB Pericarditis</td>
<td>This form of TB is characterized by an increase in the amount of fluid around the heart, and could also hamper its function.</td>
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2.3 SYMPTOMS AND DIAGNOSIS

TB is a highly contagious disease that is usually transmitted by coughing and sneezing. It is only once the infection flares into the disease that the signs and symptoms of TB are experienced. This is because the symptoms take time to surface. Some of the common TB symptoms are often misunderstood to be something else. These symptoms include; cough, fever, loss of weight, loss of energy, evening rise of temperature, chest pain, difficulty with breathing, nausea, night sweats.

Classic symptoms of TB such as fever, weight loss, night sweats, sputum production and hemoptysis are more common in younger patients (Alvarez et al., 1987). But weakness, anorexia and weight loss are significantly high in elderly patients as compared to younger patients (Dijk and Rosin, 1993). Fever, cough, chest pain, sweating, hemoptysis, cavitary disease and positive purified protein derivative as well as lower levels of serum albumin and blood leucocytes were less common symptoms among elderly patients (Perez-Guzman et al., 1999; Cavalcanti-Zdo et al., 2006). Breathlessness is the most common complaint in elderly patients followed by cough/expectoration and parenchymal exudative lesion are most common radiological feature followed by cavitary lesion in elderly populations (Arora and Bedi, 1989). In addition older population had a greater prevalence of dyspnea and some concomitant conditions such as cardiovascular system (CVS) disorders, COPD, diabetes mellitus, gastrectomy and malignancies (Perez-Guim et al., 1999).

In latent TB, patients will not have any symptoms and will not be able to spread the disease to others. It is difficult to diagnose a patient having no any symptom. It is diagnosed by detecting the presence of \textit{M. tuberculosis} bacteria, abnormal chest X-ray and surgical biopsy in the patient. A complete medical examination for the diagnosis of TB would include: physical examination, chest X-ray, microbiological examination, tuberculin skin test, surgical biopsy etc.

2.3.1 Physical Examination: It is conducted in order to check the patient's general health and check other factors that could affect the treatment.

2.3.2 Chest X-ray: In active pulmonary tuberculosis, infiltrates, consolidations or cavities are often spotted in the upper lungs, with or without mediastinal or hilar
lymphadenopathy or pleural effusions. In disseminated TB it is common to find many tiny nodules throughout the lung fields. In HIV and other low immunity persons, any abnormality in the X-ray could indicate TB, or the X-ray could even appear entirely normal.

Chest X-rays may suggest TB, but are never diagnostic of TB. They are however used to rule out the possibility of TB in those patients who have tested positive to the tuberculin skin test but apart from that have no symptoms of the disease.

2.3.3 Abreugraphy: It is an alternative to the regular chest X-ray. It is a small radiographic image. Though it has a limited resolution, it is sufficient for the diagnosis of tuberculosis. It is much cheaper than the X-ray. The procedure died down a little due to the decrease of the disease but it is still used sometimes, such as for screening prisoners, immigrants etc.

2.3.4 Microbiological examination: The culturing of M. tuberculosis organisms from a specimen taken from the patient is the only definite way of diagnosing TB. If the patient is producing sputum, the sputum smears and cultures should be done for acid-fast bacilli. Fluorescence microscopy is the preferred method to go about this. If no sputum is being produced, the specimen can be obtained by inducing sputum, genital warts, laryngeal swab, bronchoscopy with bronchoalveolar lavage, or fine needle aspiration of a collection.

There are other mycobacteria too which are acid-fast. If the smear is positive, PCR or gene probe tests can confirm the M. tuberculosis. Even if the smear shows negative, TB is still not ruled out, and is only excluded once the cultures show negative too.

2.3.5 Tuberculin Skin Test: There are two tests:

- Mantoux Skin Test: It is used in the U.S.A. It is endorsed by the American Thoracic Society and Centre’s for Disease Control. If a person tests positive to this test, then there is no requirement for any other skin test.
- Heaf Test: It was used in the UK till 2005, and is graded on a four point scale. Now the mantoux skin test is used.

An induration of the skin of more than 5-15 mm to 10 Mantoux units is considered to be a positive test for TB, indicating the presence of the TB infection.
Whenever someone is diagnosed with active form of TB, everyone in close contact with them must be screened, because TB is a deadly and infectious disease. If it is not treated in time, it could be fatal. Mortality rate is only 5%, if treated whereas if it is left untreated, 2 out of every 3 infected people will die. Therefore it is very important for a person affected by this disease to seek right treatment, and for that awareness is a must.

2.4 REVISED NATIONAL TUBERCULOSIS CONTROL PROGRAMME

In 1992, the Government of India, together with the World Health Organization (WHO) and Swedish International Development Agency (SIDA), reviewed the national programme and concluded that it suffered from managerial weakness, inadequate funding, over-reliance on X-ray, non-standard treatment regimens, low rates of treatment completion, and lack of systematic information on treatment outcomes. As a result, a Revised National Tuberculosis Control Programme (RNTCP) was designed with the following component of the DOTS strategy for the TB control:

- Political commitment by raising funds through international assistance
- Creation of a TB Unit at the sub-district level with mobile supervisory staff
- Quality diagnostic microscopy network
- Provision of blister packs anti-TB drugs in colour coded treatment boxes
- Directly Observed Treatment
- Accountability in the form of systematic monitoring and supervision from national to the peripheral level.

RNTCP adopted strategy, as the most systematic and cost effective approach to revitalise the TB control in India. The objective of RNTCP are to achieve at least 85% cure rate among the new smear-positive cases initiated on treatment and therefore a case detection of at least 70% of such cases (Verma et al., 2008). In 1993, the RNTCP was pilot-tested as phase-I project covering a population of about 18 million and over all in a population of 2.35 million at five states of India such as Delhi, Gujarat, Kerala, Maharashtra, and west Bengal. Following the successful implementation of the programme at these sites, the RNTCP was expanded and implemented to cover whole country in a phase manner (Zhang, 2004).
The RNTCP is an application of the WHO-recommended Directly Observed Treatment, Short-course (DOTS) strategy to control TB (WHO, 1994).

Five components of DOTS strategy:

- Political and administrative commitment at all level. This ensures availability of adequate funds, staff and other key inputs (Pinet, 2001).
- Diagnosis through quality sputum microscopy of symptomatic patients attending peripheral health facilities. Binocular microscopes are supplied to all RNTCP areas and regular quality assurance of the RNTCP sputum microscopy services is conducted (http://www.who.int).
- Uninterrupted supply of short-course chemotherapy (UCC) drugs, which are given in patients-wise boxes. The use of patient-wise box – an innovation of the RNTCP, which contains the entire course of treatment for an individual patient – has ensured that no patients can ever stop treatment for lack of medicines (Global Drug Facility, 2005).
- Direct observation of every dose of treatment in the intensive phase and at least the first dose of every week in the continuation phase of treatment. This has been made possible through the involvement of peripheral health functionaries, NGOs and community volunteers as DOT providers (WHO, 2009);
- Systematic supervision, monitoring and evaluation of the programme at all levels. Every quarter, the RNTCP analyses performance of the programme in every district, every state and the country as a whole. In addition to supervision by the central, state and districts level, special supervisory staff has been posted at the sub-district level (TB Unit) for this purpose (WHO, 2009).

2.4.1 Diagnosis under RNTCP

Studies conducted in the 1970s by NTI, Bangalore, demonstrated that nearly 70 percent of the cases diagnosed and put on treatment on the basis of X-ray alone did not have tuberculosis at all (Gothi et al., 1974).

The proportion of cases diagnosed on the basis of X-ray alone and put on treatment unnecessarily, is likely to be even higher in many centres. The IUATLD International Study on X-ray classification demonstrated high levels of disagreement among experts on...
the interpretation of chest radiographs (Nyboe, 1968). Furthermore, NTI also
demonstrated the ability of the laboratory technicians to perform sputum smear
microscopy effectively in the periphery, if they are given minimal training and regular
supervision (Rao et al., 1971; Nagpaul et al., 1968). Based on these studies, sputum
microscopy is used as the primary means of diagnosis under the programme and modular
training is provided to all laboratory technicians involved in RNTCP diagnostic activities.

2.4.2 Management Actions taken for Patients with Symptoms
All patients with chest symptoms (i.e., three weeks of cough) or other symptoms
suggestive of TB are advised to undergo three sputum examinations for acid-fast bacilli.
Patients with two or three positive smear results are diagnosed as having sputum smear-
positive pulmonary TB and are started on the appropriate treatment. Those with only one
positive result of the three smear examinations performed, are advised to get a chest X-
ray done and, if found to be compatible with TB, are also treated as sputum smear-
positive pulmonary TB cases. Patients, in whom all three samples are smear-negative, are
prescribed broad-spectrum antibiotic, such as co-trimoxazole, for 10-14 days. If not
suffering from TB, most patients are likely to improve with antibiotics. However if the
symptoms persist after the course of broad-spectrum antibiotics, the patient is re-
evaluated on the basis of repeat sputum examination and X-ray. Thereafter, if in the
opinion of the treating physician, the patient is suffering from tuberculosis, treatment is
initiated accordingly (Figure 1).
Figure 1: Diagnostic Algorithm for Pulmonary Tuberculosis
2.5 TREATMENT UNDER RNTCP

India has also contributed to a significant degree to pioneering research into the treatment of tuberculosis. The necessity and feasibility of treatment supervision in the community – now called DOTS and the efficacy of intermittent chemotherapy for TB as a means to simplify treatment observation for patients and for providers were demonstrated in studies conducted at TRC, Chennai (Fox, 1962; Tuberculosis Chemotherapy Centre, 1964). These scientific findings formed the basis for the decision to adopt intermittent, short course chemotherapy regimens given under direct observation as the treatment norm under the RNTCP. The patient categorization and treatment regimens (Tables 2) and definitions used under the RNTCP (Table 3).

Table 2: Treatment Regimen (Managing the Revised National Tuberculosis Control Programme in your area, 2005)

<table>
<thead>
<tr>
<th>CATEGORY OF TREATMENT</th>
<th>TYPE OF PATIENTS</th>
<th>REGIMEN*</th>
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<tbody>
<tr>
<td>Category I</td>
<td>New sputum smear-positive PTB</td>
<td>2H3R3Z3E3</td>
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<tr>
<td></td>
<td>new sputum smear-negative PTB, seriously ill**</td>
<td>4H3R3</td>
</tr>
<tr>
<td></td>
<td>new extra-pulmonary PTB, seriously ill**</td>
<td></td>
</tr>
<tr>
<td>Category II</td>
<td>Sputum smear-positive Relapse</td>
<td>2H3R3Z3E3S3</td>
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<tr>
<td></td>
<td>Sputum smear-positive treatment Failure</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Sputum smear-positive treatment after Default</td>
<td>1H3R3Z3E3</td>
</tr>
<tr>
<td></td>
<td>Others***</td>
<td>5H3R3 E3</td>
</tr>
<tr>
<td>Category III</td>
<td>New sputum smear-negative, not seriously ill</td>
<td>2H3R3Z3</td>
</tr>
<tr>
<td></td>
<td>New extra-PTB, not seriously ill</td>
<td>4H3R3</td>
</tr>
</tbody>
</table>

* The number before the letters refers to the number of months of treatment. The subscript after the letters refers to the doses per week. The dosage strengths are as follows: H: Isoniazid (600 mg), R: Rifampicin (450 mg), Z: Pyrazinamide (1500 mg), E: Ethambutol (1200 mg), S: Streptomycin (750 mg). Patients who weigh 60 kg or more receive additional rifampicin 150 mg. Patients who are more than 50 years old receive streptomycin 500 mg. Patients who weigh less than 30 kg receive drugs as per body weight. Patients in Categories I and II who have a positive sputum smear at the end of the initial intensive phase receive an additional month of intensive phase treatment.

** Seriously ill also includes, any patient, pulmonary or extra-pulmonary who is HIV positive and declares his sero-status to the categorizing/treating medical officer. For the purpose of categorization, HIV testing should not be done.

*** In rare and exceptional cases, patients who are sputum smear-negative or who have extra-pulmonary disease can have Relapse or Failure. This diagnosis in all such cases should always be made by a MO and should be supported by culture or histological evidence of current, active TB. In these cases, the patient should be categorized as ‘Others’ and given Category II treatment.
### Table 3: Definitions used under the RNTCP (Managing the Revised National Tuberculosis Control Programme in your area, 2005)

<table>
<thead>
<tr>
<th>Case definitions</th>
<th>Types of cases</th>
<th>Treatment outcome</th>
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<tbody>
<tr>
<td><strong>Pulmonary Tuberculosis, Smear-positive</strong>&lt;br&gt; TB in a patient with at least 2 initial sputum smear examinations (direct smear microscopy) positive for AFB.&lt;br&gt; Or: TB in a patient with one sputum smear examination positive for AFB and radiographic abnormalities consistent with active pulmonary TB as determined by the treating MO&lt;br&gt; Or: TB in a patient with one sputum smear specimen Positive for AFB and culture positive for <em>M. tuberculosis.</em>&lt;br&gt;</td>
<td><strong>New</strong>&lt;br&gt; A TB patient who has never had treatment for tuberculosis or has taken anti-tuberculosis drugs for less than one month.&lt;br&gt; <strong>Relapse</strong>&lt;br&gt; A TB patient who was declared cured or treatment completed by a physician, but who reports back to the health service and is now found to be sputum smear positive.&lt;br&gt;</td>
<td><strong>Treatment completed</strong>&lt;br&gt; Sputum smear-positive patient who has completed treatment, with negative smears at the end of the intensive phase but none at the end of treatment.&lt;br&gt; Or: Sputum smear-negative TB patient who has received a full course of treatment and has not become smear-positive during or at the end of treatment.&lt;br&gt; Or: Extra-pulmonary TB patient who has received a full course of treatment and has not become smear-positive during or at the end of treatment.&lt;br&gt;</td>
</tr>
<tr>
<td><strong>Pulmonary Tuberculosis, Smear-negative</strong>&lt;br&gt; TB in a patient with symptoms suggestive of TB with at least 3 sputum smear examinations negative for AFB, and radiographic abnormalities consistent with active pulmonary TB as determined by the treating MO followed by a decision to treat the patient with a full course of anti-tuberculosis therapy&lt;br&gt; Or: Diagnosis based on positive culture but negative AFB sputum smear examinations.&lt;br&gt;</td>
<td><strong>Transferred in</strong>&lt;br&gt; A TB patient who has been received for treatment into a Tuberculosis Unit, after starting treatment in another Unit where s/he has been registered.&lt;br&gt; <strong>Treatment after default</strong>&lt;br&gt; A TB patient who received antituberculosis treatment for one month or more from any source and returns to treatment after having defaulted, i.e., not taken anti-TB drugs consecutively for two months or more, and is found to be sputum smear positive.&lt;br&gt;</td>
<td><strong>Cured</strong>&lt;br&gt; Initially sputum smear-positive patient who has completed treatment and had negative sputum smears, on two occasions, one of which was at the end of treatment.&lt;br&gt; <strong>Died</strong>&lt;br&gt; Patient who died during the course of treatment regardless of cause&lt;br&gt; <strong>Defaulted</strong>&lt;br&gt; A patient who has not taken anti-TB drugs for 2 months or more consecutively after starting treatment.&lt;br&gt;</td>
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<tr>
<td><strong>Extra Pulmonary Tuberculosis</strong>&lt;br&gt; TB of any organ other than the lungs, such as the pleura (TB pleurisy), lymph nodes, intestines, genitourinary tract, skin, joints and bones, meningitis of the brain etc.&lt;br&gt; Diagnosis should be based on culture-positive specimen from the extra-pulmonary site, histological, radiological, or strong clinical evidence consistent with active extra pulmonary TB followed by decision of the treating MO to treat with a full course of anti-TB therapy.&lt;br&gt; Pleurisy is classified as extra pulmonary TB. A patient diagnosed with both sputum smear positive pulmonary and extra pulmonary TB should be classified as pulmonary TB.&lt;br&gt;</td>
<td><strong>Failure</strong>&lt;br&gt; Any TB patient who is smear positive at 5 months or more after starting treatment. Failure also includes a patient who was treated with Category III regimen but who becomes smear positive during treatment.&lt;br&gt; <strong>Chronic</strong>&lt;br&gt; A TB patient who remains smear positive after completing a re-treatment regimen.&lt;br&gt; <strong>Others</strong>&lt;br&gt; TB patients who do not fit into the above mentioned types. Reasons for putting a patient in this type must be specified.&lt;br&gt;</td>
<td><strong>Failure</strong>&lt;br&gt; Any TB patient who is smear positive at 5 months or more after starting treatment. Failure also includes a patient who was treated with Category III regimen but who becomes smear positive during treatment.&lt;br&gt; <strong>Transferred out</strong>&lt;br&gt; A patient who has been transferred to another tuberculosis Unit/District and his/her treatment result (outcome) is not known.&lt;br&gt;</td>
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*Department of Pharmacology*
All RNTCP treatment regimens are given thrice weekly on alternate days. During the intensive phase, each dose of medication is packed in blister packs containing one day’s medication and is given under the direct observation of a DOT provider. During the continuation phase, medication is packed in weekly blister packs, with the first of the thrice weekly doses being given under direct observation of DOT provider. Patients treated with Category I and II regimens, whose smears are positive at the end of the intensive phase, are given another month of intensive phase treatment before being started on the continuation phase treatment.

Even where the drug supply is ensured, direct observation of treatment is necessary as it has been shown that treatment without direct observation results in, at best, a 60 percent treatment success, compared with the 85-95 percent with direct observation of treatment (Balasubramaniam et al., 2000). These results were observed despite the uninterrupted availability of free anti-TB medications in both groups of patients. Treatment observation is an activity that supports the patient to take every dose of medication for the required duration of treatment and thus ensures cure. It is important to emphasise that treatment observation is not meant to be a mechanical, unfeeling activity but the creation of a meaningful relationship and a human bond between the patient and the treatment observer, whereby patients are reliably cured.

All attempts are made to locate DOT centres close to patients home. To ensure accessibility, different kinds of DOT providers have been trained and utilised by the RNTCP. The only criteria for becoming a DOT provider is that he/she should be acceptable to the patient and accountable to the health system. DOT providers include the staff of the health system (hospitals, clinics, Auxiliary Nurse and Midwife, pharmacists, etc), staff of NGOs, private practitioners, community volunteers, religious leaders, anganwadi workers, dais, etc. However, the programme discourages the use of family members as they have not been found to be effective treatment observers.
2.6 TREATMENT

The standard treatment for Active TB is Isoniazid, Rifampicin, Pyrazinamine, and Ethambutol for a period of two months followed by isoniazid and rifampicin for a further four months. At the end of this 6 month period, the patient is said to be cured, but a 2-3% chance of relapse is possible. For Latent TB, the standard treatment is isoniazid alone for a period of 6-9 months.

Patient compliance is an important issue in the treatment of TB, because symptoms will go off in a few weeks to month. But for the complete removal of mycobacterium for the patients needs to continue their medication up to full course. The TB bacterium is a very slow dieing one, and takes a minimum of 6 months for all the bacteria to die with the medicines.

Isoniazid and Ethambutol are bacteriostatic, they stop the bacterial growth, where as Rifampicin is bacteriocidal, it kills the bacteria.

ISONIAZID

Description

Isoniazid is chemically isonicotinic acid hydrazide or synthetic pyridine derivative of nicotinamide (Fox, 1952). It is a colourless, odourless, white crystalline powder, slowly affected by exposure to air and light. It is freely soluble in water, sparingly soluble in alcohol and slightly soluble in chloroform and very slightly soluble in ether. A 10% solution has a pH of 6.0 to 8.0. The solution for parenteral injection is a clear, colourless liquid. Its molecular formula is C_{6}H_{7}N_{3}O & its molecular weight is 137.14 (Fox, 1952).

Antibacterial Activity

Isoniazid is bacteriostatic for "resting" bacilli, but is bactericidal for rapidly dividing microorganisms. The minimal tuberculostatic concentration ranges from 0.025 - 0.05 µg/ml. Before multiplication is arrested, mycobacteria undergo one or two divisions only. The drug is highly selective for mycobacteria, and concentrations upto 500 µg/ml are required to inhibit the growth of other microorganisms (Jayaram et al., 2004).

Isoniazid is strikingly superior to streptomycin and is highly effective for the treatment of experimentally induced tuberculosis in animals. Unlike streptomycin, isoniazid penetrates
cells with ease and is just as effective against bacilli growing within cells as it is against those growing in culture media. (Gumbo et al., 2007)

Bacterial Resistance
When tubercle bacilli are grown in-vitro in increasing concentrations of isoniazid, mutants are readily selected that are resistant to the drug. The shift from primarily sensitive to mainly insensitive microorganisms occasionally occurs within a few weeks after therapy is started; however, the time of appearance of isoniazid resistance varies considerably from one case to another. Approximately 1 in 106 tubercle bacilli will be genetically resistant to isoniazid; since tuberculous cavities may contain as many as 107 to 109 microorganisms, it is not surprising that treatment with isoniazid alone selects for these resistant bacteria. The incidence of primary resistance to isoniazid in the United States until recently had been fairly stable at 2% to 5% of isolates of \emph{M. tuberculosis}. Resistance currently is estimated at 8% of isolates, but may be much higher in certain populations, including Asian and Hispanic immigrants and in large urban areas and coastal or border communities (Iseman, 1993; Advisory Council for the Elimination of Tuberculosis, 1999).

Mechanism of Action
Isoniazid is a prodrug; mycobacterial catalase-peroxidase converts isoniazid into an active metabolite. A primary action of isoniazid is to inhibit the biosynthesis of mycolic acids long branched lipids that are attached to a unique polysaccharide, arabino galactan, to form part of the mycobacterial cell wall. The mechanism of action of isoniazid is complex, with resistance mapping to mutations in at least five different genes (\text{katG} [coding for the catalase-peroxidase that activates the prodrug isoniazid], \text{inhA}, \text{ahpC}, \text{kasA}, and \text{ndh}). The preponderance of evidence points to \text{inhA} as the primary drug target. Indeed, the catalase-peroxidase-activated isoniazid, but not the prodrug, binds to the \text{inhA} gene product enoyl-ACP reductase of fatty acid synthase II, which converts unsaturated fatty acids to saturated fatty acids in the mycolic acid biosynthetic pathway (Vilcheze et al., 2000; De La Iglesia and Morbidoni, 2006). Mycolic acids are unique to mycobacteria, explaining the high degree of selectivity of the antimicrobial activity of isoniazid. Mutations of the \text{katG} gene that result in an inactive catalase-peroxidase cause
high-level isoniazid resistance, since the prodrug cannot be activated by the catalase-peroxidase (Blanchard, 1996). Isoniazid also inhibits mycobacterial catalase-peroxidase (the isoniazid-activating enzyme), which may increase the likelihood of damage to the mycobacteria from reactive oxygen species and $H_2O_2$. Exposure to isoniazid leads to a loss of acid-fastness and a decrease in the quantity of methanol-extractable lipids in the microorganisms.

**Absorption, Distribution, and Excretion**

After oral administration, isoniazid is readily absorbed from the GI tract and produces peak blood levels of 3 to 5 $\mu$g/ml within 1 to 2 hours. Aluminum-containing antacids may interfere with absorption. It diffuses readily into all body fluids (cerebrospinal, pleural, and ascitic fluids), tissues, organs, and excreta (saliva, sputum, and feces). Concentrations in the cerebrospinal fluid (CSF) with inflamed meninges are similar to those in the plasma (Holdiness, 1985). Isoniazid is not substantially bound to plasma proteins. The drug also passes through the placental barrier and into milk in concentrations comparable to those in the plasma. The concentration of the agent is initially higher in the plasma and muscle than in the infected tissue, but the latter retains the drug for a long time in quantities well above those required for bacteriostasis.

The plasma half-life of isoniazid in patients with normal renal and hepatic function ranges from 1-4 hours, depending on the rate of metabolism. In slow and fast acetylators 50% – 70% and 75 – 90% of a dose of isoniazid is excreted in the urine within 24 hours, mostly as metabolites respectively (Rifater, 2009). Isoniazid is metabolized in the liver mainly by acetylation (acetylisoniazid) and hydrolysis (isonicotinic acid). Small quantities of an isonicotinic acid conjugate (probably isonicotinyl glycine), one or more isonicotinyl hydrazones, and traces of N-methylisoniazid also are detectable in the urine. The rate of acetylation is genetically determined but does not significantly alter the effectiveness of isoniazid. However, slow acetylation may lead to higher blood levels of the drug, and thus, an increase in toxic reactions. Approximately 50% of African Americans and Caucasians are “slow inactivators” and the rest are “rapid inactivators”; the majority of Eskimos and Asians are “rapid inactivators.” Pyridoxine (B6) deficiency is sometimes observed in adults with high doses of isoniazid and is probably due to its
competition with pyridoxal phosphate for the enzyme apo-tryptophanase. (Hall et al., 2009)

The distribution of slow and rapid inactivators of the drug is bimodal owing to differences in the levels and activity of the genetically polymorphic arylamine $N$-acetyltransferase type 2 (NAT2). The activity of NAT2 enzyme translated from variant alleles is decreased mostly by the impaired stability or a decrease in $V_{max}$. At least 36 NAT2 alleles have been identified, although many may not be clinically important (Schippers et al., 2005). As an autosomal recessive trait, only individuals bearing two variant alleles are expected to be prone to impaired acetylation capacity (Meisel, 2002). The rate of acetylation significantly alters the concentrations of the drug that are achieved in plasma and its half-life in the circulation. The half-life of the drug may be prolonged by hepatic insufficiency.

In the whole population, the half-life of isoniazid varies from less than 1 to more than 4 hours. The mean half-life in fast acetylators is approximately 70 minutes, whereas 2 to 5 hours is characteristic of slow acetylators. Because isoniazid is relatively nontoxic, a sufficient amount of drug can be administered to fast acetylators to achieve a therapeutic effect equal to that seen in slow acetylators. A dosage reduction is recommended for slow acetylators with hepatic failure. The clearance of isoniazid is dependent only to a small degree on the status of renal function, but patients who are slow inactivators of the drug may accumulate toxic concentrations if their renal function is impaired (Rifater, 2009).

**Precautions**

All drugs should be stopped and an evaluation of the patient should be made at the first sign of a hypersensitivity reaction. Isoniazid, should be carefully monitored in the following:

1. Patients who are receiving phenytoin (diphenylhydantoin) concurrently because it may decrease the excretion of phenytoin or may enhance its effects. Therefore appropriate adjustment of the anticonvulsant dose should be made to avoid intoxication.
2. Daily users of alcohol because it may be associated with a higher incidence of isoniazid hepatitis.
3. Patients with current chronic liver disease or severe renal dysfunction.
Adverse Effects

The incidence of adverse reactions to isoniazid was estimated to be 5.4% among more than 2000 patients treated with the drug; the most prominent of these reactions were rash (2%), fever (1.2%), jaundice (0.6%), and peripheral neuritis (0.2%).

Hypersensitivity to isoniazid may result in fever, various skin eruptions, hepatitis, and morbilliform, maculopapular, purpuric, and urticarial rashes. Hematological reactions also may occur (agranulocytosis; eosinophilia; thrombocytopenia; hemolytic, sideroblastic, or aplastic anemia). Vasculitis associated with antinuclear antibodies may appear during treatment but disappears when the drug is stopped. Arthritic symptoms (back pain; bilateral proximal interphalangeal joint involvement; arthralgia of the knees, elbows, and wrists; and the "shoulder-hand" syndrome) have been attributed to this agent.

Gastrointestinal system adverse events include nausea, vomiting, and epigastric distress. Peripheral neuropathy (paresthesia of the feet and hands) is the most common toxic effect of isoniazid and occurs in about 2% of patients. It is dose-related, more frequent in slow acetylators, and occurs most often in the malnourished and in those predisposed to neuritis (eg, alcoholics and diabetics). Higher doses may result in peripheral neuritis in 10% to 20% of patients. The prophylactic administration of pyridoxine prevents the development not only of peripheral neuritis, but also of most other nervous system disorders in practically all instances, even when therapy lasts as long as 2 years. Other neurotoxic effects, which are uncommon with conventional doses, are convulsions, toxic encephalopathy, optic neuritis and atrophy, memory impairment, and toxic psychosis. Isoniazid may precipitate convulsions in patients with seizure disorders, and rarely, in patients with no history of seizures. Optic neuritis and atrophy also have occurred during therapy with the drug. Muscle twitching, dizziness, ataxia, paresthesias, stupor, and toxic encephalopathy that may be fatal are other manifestations of the neurotoxicity of isoniazid. A number of mental abnormalities may appear during the use of this drug, including euphoria, transient impairment of memory, separation of ideas and reality, loss of self-control, and florid psychoses.

Isoniazid is known to inhibit the parahydroxylation of phenytoin, and signs and symptoms of toxicity occur in approximately 27% of patients given both drugs, particularly in those who are slow acetylators (Miller et al., 1979). Concentrations of
phenytoin in plasma should be monitored and adjusted if necessary. The dosage of isoniazid should not be changed.

Although jaundice has been known for some time to be an untoward effect of exposure to isoniazid, not until the early 1970s did it become apparent that severe hepatic injury leading to death may occur in some individuals receiving this drug (Garibaldi et al., 1972). Additional studies in adults and children have confirmed this observation; the characteristic pathological process is bridging and multilobular necrosis. Continuation of the drug after symptoms of hepatic dysfunction have appeared tends to increase the severity of damage. The mechanisms responsible for this toxicity are unknown, although acetylhydrazine, which is a metabolite of isoniazid, causes hepatic damage in adults.

Hence, patients who are rapid acetylators of isoniazid might be expected to be more likely to develop hepatotoxicity than slow acetylators; whether this is true, however, is unresolved. A contributory role of alcoholic hepatitis has been noted, but chronic carriers of the hepatitis B virus tolerate isoniazid (McGlynn et al., 1986). Age appears to be the most important factor in determining the risk of isoniazid-induced hepatotoxicity. Hepatic damage is rare in patients less than 20 years old; the complication is observed in 0.3% of those 20 to 34 years old, and the incidence increases to 1.2% and 2.3% in individuals 35 to 49 and older than 50 years of age, respectively (Bass et al., 1994; Comstock, 1983). Up to 12% of patients receiving isoniazid may have elevated plasma aspartate and alanine transaminase activities (Bailey et al., 1974). Patients receiving isoniazid should be carefully evaluated at monthly intervals for symptoms of hepatitis (anorexia, malaise, fatigue, nausea, and jaundice) and warned to discontinue the drug if such symptoms occur. Some clinicians also prefer to determine serum aspartate aminotransferase activities at monthly intervals in high-risk individuals (ages 7 to 35, excessive alcohol intake, history of liver disease, etc.) (Byrd et al., 1979), and recommend that an elevation greater than five times normal is cause for drug discontinuation. Most hepatitis occurs 4 to 8 weeks after the start of therapy. Isoniazid should be administered with great care to those with preexisting hepatic disease.

Among miscellaneous reactions associated with isoniazid therapy are dryness of the mouth, epigastric distress, methemoglobinemia, tinnitus, and urinary retention. In persons predisposed to pyridoxine-deficiency anemia, the administration of isoniazid may result
in dramatic anemia, but treatment with large doses of vitamin B6 gradually returns the blood to normal in such cases. A drug-induced syndrome resembling systemic lupus erythematosus has also been reported.

Overdosage
Isoniazid 1.5g ingested acutely, may cause toxicity in adults. Untreated or inadequately treated cases of gross isoniazid overdosage can be fatal, but good response has been reported in most patients treated within the first few hours after drug ingestion.

Isoniazid as in attempted suicide produces signs and symptoms within 30 minutes to 3 hours. Nausea, vomiting, dizziness, slurred speech, and visual hallucinations are among the early manifestations. With marked overdosage, respiratory distress and CNS depression progressing rapidly from stupor to profound coma are to be expected along with severe, intractable seizures. Doses of 35 to 40 mg/kg have resulted in seizures. Ingestion of 80 to 150 mg/kg isoniazid has been associated with severe toxicity and, if untreated, significant mortality. Severe metabolic acidosis, acetonuria, and hyperglycemia are typical laboratory findings. Pyridoxine is an antidote in this setting; it should be given in a dose that approximates the amount of isoniazid ingested. Pyridoxine, vitamin B6, (10 to 50 mg per day) should be administered with isoniazid to minimize the risks of peripheral neuropathy and central nervous system toxicity in malnourished patients and those predisposed to neuropathy (e.g., the elderly, pregnant women, HIV-infected individuals, diabetics, alcoholics, and uremics) (Snider, 1980).
RIFAMPICIN (RIFAMPIN)

Description
Rifamycins (rifampin, rifabutin, rifapentine) are a group of structurally similar complex macrocyclic antibiotics produced by *Amycolatopsis mediterranei* (Farr, 2000); rifampin is a semisynthetic antibiotic derivative of these rifamycin B. Rifampins were first isolated by Lepetit Research Laboratories from cultures obtained from a pine forest near Nice, France (Vernon, 2004). Rifampin is an odourless, red-brown crystalline powder very slightly soluble in water at neutral pH, freely soluble in chloroform, soluble in ethyl acetate and methanol at acidic pH. A 1% suspension in water has pH 4.5 to 6.5. Rifampicin has 2 pKa since it is a Zwitterion, pKa 1.7 related to 4-hydroxy and pKa 7.9 related to 3-piperazine nitrogen. Its molecular weight is 822.95 and its chemical formula is C_{43}H_{58}N_{4}O_{12}.

Antibacterial Activity
Rifampin inhibits the growth of most gram-positive bacteria as well as many gram-negative microorganisms such as *Escherichia coli*, *Pseudomonas*, indole-positive and indole-negative *Proteus*, and *Klebsiella*. Rifampin is very active against *Staphylococcus aureus* and coagulase-negative *staphylococci*. The drug also is highly active against *Neisseria meningitidis* and *Haemophilus influenzae*; minimal inhibitory concentrations range from 0.1 to 0.8 μg/ml. Rifampin inhibits the growth of *Legionella species* in cell culture and in animal models.

Rifampin in concentrations of 0.005 to 0.2 μg/ml inhibits the growth of *M. tuberculosis* in vitro. Among nontuberculous mycobacteria, *M. kansasii* is inhibited by 0.25 to 1 μg/ml. The majority of strains of *M. scrofulaceum*, *M. intracellulare*, and *M. avium* are suppressed by concentrations of 4 μg/ml, but certain strains may be resistant to 16 μg/ml. *M. fortuitum* is highly resistant to the drug. Rifampin increases the in vitro activity of streptomycin and isoniazid, but not that of ethambutol, against *M. tuberculosis*.

Bacterial Resistance
Microorganisms, including mycobacteria, may develop resistance to rifampin rapidly in vitro as a one-step process, and one of every 107 to 108 tubercle bacilli is resistant to the drug. Microbial resistance to rifampin is due to an alteration of the target of this drug.
DNA-dependent RNA polymerase, with resistance in most cases being due to mutations between codons 507 and 533 of the polymerase rpoB gene (Blanchard, 1996); the mutations reduce binding of the drug to the polymerase. As a consequence, the antibiotic must not be used alone in the chemotherapy of tuberculosis. When rifampin has been used to eradicate the meningococcal carrier state, failures have been due to the appearance of drug-resistant bacteria after treatment for as few as 2 days. Certain rifampin-resistant bacterial mutants have decreased virulence. Tuberculosis caused by rifampin-resistant mycobacteria has been described in patients who had not received prior chemotherapy, but this is very rare i.e. usually < 1% (Cauthen et al., 1988).

**Mechanism of Action**

Rifampin is bactericidal for both intracellular and extracellular microorganisms. It inhibits DNA-dependent RNA polymerase of mycobacteria and other microorganisms by forming a stable drug-enzyme complex, leading to suppression of initiation of chain formation (but not chain elongation) in RNA synthesis. More specifically, the β subunit of this complex enzyme is the site of action of the drug, although rifampin binds only to the holoenzyme. Nuclear RNA polymerases from a variety of eukaryotic cells do not bind rifampin, and RNA synthesis is correspondingly unaffected in eukaryotic cells. High concentrations of rifamycin antibiotics can inhibit RNA synthesis in mammalian mitochondria, viral DNA-dependent RNA polymerases, and reverse transcriptases (Molavi, 1990).

**Absorption, Distribution, and Excretion**

After oral administration rifampicin is readily absorbed (90%) from gastrointestinal tract and produces peak concentrations in plasma in 2 to 4 hours; after administration of 450 mg oral dose, plasma level reach 6 to 9 µg/ml while a 600mg dose, produces peak concentration of 4 to 32 µg/ml (mean 7 µg/ml) in fasted condition. Food may delay absorption (Mandell and Sande, 1985; Ellenhorn and Barceloux, 1988). Aminosalicylic acid may delay the absorption of rifampin and leads to failure of therapy. If aminosalicylate and rifampin are used concurrently, they should be given separately at an interval of 8 to 12 hours.
Intravenous rifampicin has the same distribution as in oral route. It is lipid soluble 90% of rifampicin in circulation is bound to plasma proteins (Gilman et al., 1990).

Rifampin is widely distributed throughout the body and is present in effective concentrations in many organs and body fluids, including the CSF (Van Scoy and Wilkowske, 1987). This is perhaps best exemplified by the fact that the drug may impart an orange-red color to the urine, feces, saliva, sputum, tears, and sweat; patients should be so warned (Furesz, 1970; Farr, 2000).

Rifampicin has a high degree of placental transfer with a foetal to maternal serum level ratio of 0.3. It is distributed into breastmilk (Chow and Jesesson, 1985).

**Biological half life**

Half life of rifampicin range from 2 to 5 hours and is increased by hepatic dysfunction. The half-life lower by 40% during the first two weeks of therapy because of enhanced biliary excretion and induction of its own metabolism. Plasma half-life may decrease after repeated administration. The half-life of rifampicin decreased from 3.5 hours at start of therapy to 2 hours after daily administration for 1 to 2 weeks, and remained constant thereafter (Molavi, 1990). Plasma half-life shortens to 1.8 to 3.1 hours in the presence of anaemia.

**Metabolism**

Approximately 85% of rifampicin is metabolised by the liver microsomal enzymes to its main and active metabolite-deacetyl rifampicin. Rifampicin undergoes enterohepatic recirculation but not the deacetylated form. Rifampicin increases its own rate of metabolism.

**Elimination**

Rifampicin metabolite deacetyl rifampicin is excreted in the bile and also in the urine. Approximately 50% of the rifampicin dose is eliminated within 24 hours and 6 to 30% of the drug is excreted unchanged in the urine, while 15% is excreted as active metabolite. Approximately 43 to 60% of oral dose is excreted in the faeces (Van Scoy and Wilkowske, 1987). Adjustment of dosage is not necessary in patients with impaired renal function. Rifampicin is excreted in breastmilk (1 to 3 μg/ml).
Precaution
For treatment of tuberculosis, rifampin is usually administered on a daily basis. Doses of rifampin (>600 mg) given once or twice weekly have resulted in a higher incidence of adverse reactions, including the “flu syndrome” (fever, chills and malaise); hematopoietic reactions (leukopenia, thrombocytopenia, or acute hemolytic anemia); cutaneous, gastrointestinal, and hepatic reactions; shortness of breath; shock and renal failure. The patient should be advised that the reliability of oral contraceptives may be affected; consideration should be given to using alternative contraceptive measures.

Adverse Events
Rifampin generally is well tolerated. Fewer than 4% of patients with tuberculosis developed significant adverse reactions, when given in usual doses; the most common are rash (0.8%), fever (0.5%), and nausea and vomiting (1.5%) (Grosset and Leventis, 1983). Rifampicin causes cholestasis at both the sinusoids and canaliculi of the liver because of defect in uptake by hepatocytes and defect in excretion, respectively. Hepatitis (≤1%) and deaths have been reported (due to liver failure) in patients who received other hepatotoxic agents in addition to rifampin, or who had preexisting liver disease. Hepatitis from rifampin rarely occurs in patients with normal hepatic function; likewise, the combination of isoniazid and rifampin appears generally safe in such patients (Gangadharam, 1986). In patients with previously deranged liver condition, patients may develop clinical jaundice and a more severe liver damage may ensue. However, chronic liver disease, alcoholism, and old age appear to increase the incidence of severe hepatic problems when rifampin is given alone or concurrently with isoniazid.

Nephrotoxicity appears to be related to a hypersensitivity reaction and usually occurs due to intermittent or interrupted therapy developing antibodies. It has been suggested that some of the adverse effects associated with rifampicin may be attributed to its metabolite desacetylrifampicin.

Gastrointestinal disturbances produced by rifampin (epigastric distress, nausea, vomiting, abdominal cramps, diarrhea) have occasionally required discontinuation of the drug. Various symptoms related to the nervous system also have been noted, including fatigue, drowsiness, headache, dizziness, ataxia, confusion, inability to concentrate, generalized numbness, pain in the extremities, and muscular weakness. Hypersensitivity reactions
include fever, pruritus, urticaria, various types of skin eruptions, eosinophilia, and soreness of the mouth and tongue reported in 20% of patients. Hemolysis, hemoglobinuria, hematuria, renal insufficiency, and acute renal failure have been observed rarely; these also are thought to be hypersensitivity reactions. Thrombocytopenia, transient leukopenia, and anemia have occurred during therapy. Since the potential teratogenicity of rifampin is unknown and the drug is known to cross the placenta, it is best to avoid the use of this agent during pregnancy (Graber et al., 1973) noted immunoglobulin light-chain proteinuria (either kappa, lambda, or both) in about 85% of patients with tuberculosis treated with rifampin. None of the patients had symptoms or electrophoretic patterns compatible with myeloma. However, renal failure has been associated with light-chain proteinuria (Warrington et al., 1977).

**Overdosage**

Patients have survived after an overdose of 12 g of rifampin has been reported (Ellenhorn and Barceloux, 1988). One case of death reported with self administering overdose of 60mg rifampicin.
PYRAZINAMIDE

Description

Pyrazinamide is a pyrazine analogue of nicotinamide. It is a white, crystalline powder, stable at room temperature, and sparingly soluble in water. The chemical name for pyrazinamide is pyrazinecarboxamide and its molecular weight is 123.11. Its chemical formula is $\text{C}_5\text{H}_5\text{N}_3\text{O}$.

Antibacterial Activity

*In vitro* study shows that, pyrazinamide exhibits bactericidal activity only at a slightly acidic pH, since *M. tuberculosis* resides in an acidic phagosome within the macrophage (Jacobs, 2000). Tubercle bacilli are inhibited or killed by the drug at a concentration of 12.5 $\mu$g/ml within monocytes *in vitro*. Rapidly resistance develops when pyrazinamide is used alone. The target of pyrazinamide appears to be the mycobacterial fatty acid synthase I gene involved in mycolic acid biosynthesis (Zimhony *et al.*, 2000).

Absorption, Distribution, and Excretion

Pyrazinamide is well absorbed from the gastrointestinal tract and widely distributed after oral administration throughout the body tissues and fluids including the liver, lungs, CNS and reaches to cerebrospinal fluid (CSF). The oral administration of 500 mg produces plasma concentrations of about 9 to 12 $\mu$g/ml at 2 hours and 7 $\mu$g/ml at 8 hours. Pyrazinamide is approximately 10% bound to plasma proteins. The plasma half-life is 9 to 10 hours in patients with normal renal and hepatic function and prolonged in impaired renal and hepatic function. The drug is excreted primarily by renal glomerular filtration. Pyrazinamide is hydrolyzed to pyrazinoic acid in the liver to its major active metabolite, and subsequently hydroxylated to 5-hydroxypyrazinoic acid, the major excretory product. Approximately 70% of an oral dose of pyrazinamide is excreted in urine within 24 hours, mainly by glomerular filtration. About 4% to 14% of the dose is excreted as unchanged drug; the remainder is excreted as metabolites (Rifater, 2009).
Chapter 2

Precaution
Pyrazinamide inhibits renal excretion of urates, frequently resulting in hyperuricemia which is usually asymptomatic. If hyperuricemia is accompanied by acute gouty arthritis, pyrazinamide should be discontinued.

Adverse events
Injury to the liver is the most serious side effect of pyrazinamide. When a dose of 40 to 50 mg/kg is administered orally, signs and symptoms of hepatic disease appear in about 15% of patients, with jaundice in 2% to 3% and death due to hepatic necrosis in rare instances. Elevations of plasma alanine and aspartate aminotransferases are the earliest abnormalities produced by the drug. Regimens employed currently (15 to 30 mg/kg per day) are much safer. Prior to pyrazinamide administration all patients should undergo studies of hepatic function and these studies should be repeated at frequent intervals during the entire period of treatment. If evidence of significant hepatic damage becomes apparent, therapy must be stopped. Pyrazinamide should not be given to individuals with any degree of hepatic dysfunction unless this is absolutely unavoidable.

The drug inhibits excretion of urate, resulting in hyperuricemia in nearly all patients; acute episodes of gout have occurred. Other untoward effects that have been observed with pyrazinamide are arthralgias, anorexia, nausea and vomiting, dysuria, malaise, and fever. While some international organizations recommend the use of pyrazinamide in pregnancy, this is not the case in the United States because of inadequate data on teratogenicity (Bass et al., 1994).

Overdosage
No information of overdosage are available due to pyrazinamide. Abnormal liver function tests can develop due to pyrazinamide overdosage. It spontaneously reverts to normal when the drug was stopped.
ETHAMBUTOL

Description
Ethambutol is a synthetic oral antibiotic derivative of ethylenediamine which contains two imine radicals and two butanol radicals. It is white, crystalline hygroscopic powder, bitter taste. Its melting point is 199 °C to 204 °C. It is very slightly soluble in ether. A solution in water is dextrorotatory. Solutions are stable when heated at 121 °C for 10 minutes (Reynolds, 1993; Windholz et al., 1983). It is available in two forms i.e. base for and hydrochloride form. Molecular formula & molecular weight of base form of ethambutol are C\(_{10}\)H\(_{24}\)N\(_2\)O\(_2\) and 204.3 respectively where as of its hydrochloride forms are C\(_{10}\)H\(_{24}\)N\(_2\)O\(_2\) 2HCl and 277.2 respectively (Budavari, 1989; Reynolds, 1993).

Antibacterial Activity, Mechanism of Action, Resistance
Ethambutol is an oral chemotherapeutic agent, effective against all strains of actively growing *M. tuberculosis* and *M. kansasii* as well as a number of strains of MAC (Pablos-Mendez et al., 1998) but does not seem to be active against fungi, viruses, or other bacteria. Ethambutol is bacteriostatic and appears to inhibit the synthesis of one or more metabolites, thus causing impairment of cell metabolism, arrest of multiplication, and cell death. It suppresses the growth of most isoniazid- and streptomycin-resistant tubercle bacilli. Mycobacteria take up ethambutol rapidly when the drug is added to cultures that are in the exponential growth phase. However, growth is not significantly inhibited before about 24 hours. Ethambutol inhibits arabinosyl transferases involved in cell wall biosynthesis. Bacterial resistance to the drug develops *in vivo via* single amino acid mutations in the *embA* gene when ethambutol is given in the absence of other effective agents (Belanger et al., 1996).

Absorption, Distribution, and Excretion
After oral administration of ethambutol about 75% to 80% drug absorbed from the gastrointestinal tract and the remainder appears in the faeces unchanged. Absorption is not significantly impaired by food (Reynolds, 1993). Peak plasma concentrations of 2 to 5 \(\mu\)g/ml, attained in 2 to 4 hours after single oral dose of 25mg/kg and is less than 1 \(\mu\)g/ml by 24 hours. Ethambutol diffuses readily into red blood cells and into the
cerebrospinal fluid when the meninges are inflamed. The concentration in erythrocytes at steady state is approximately twice the plasma concentration. Protein binding is less than 5%; the volume of distribution is 1.6 L/kg (Gilman et al., 1990). It has been reported to cross the placenta and is excreted in breast milk (Reynolds, 1989). The concentration of ethambutol in one sample of breast milk collected during a 2 hour period after a dose of 15 mg per kg body-weight was 1.4 µg/ml. Another woman had simultaneous concentrations of 4.62 and 4.60 µg/ml in plasma and milk respectively, but no dose had been specified (Reynolds, 1989).

The main path of metabolism appears to be an initial oxidation of the alcohol to an aldehydic intermediate, followed by conversion to a dicarboxylic acid. During the 24-hour period following oral administration of ethambutol, approximately 50% of the initial dose is excreted unchanged in the urine, while an additional 8% to 15% appears in the form of metabolites. From 20 to 22% of the initial dose is excreted in the faeces as unchanged drug.

The drug has a half-life of 3 to 4 hours. Within 24 hours, 75% of an ingested dose of ethambutol is excreted unchanged in the urine; up to 15% is excreted in the form of two metabolites, an aldehyde and a dicarboxylic acid derivative (Gilman et al., 1990). Renal clearance of ethambutol is approximately 7 ml/min/kg; thus it is evident that the drug is excreted by tubular secretion in addition to glomerular filtration. The intrinsic total body clearance is 9 ml/min/kg (Gilman et al., 1990).

**Contraindications**

Ethambutol hydrochloride is contraindicated in patients who are known to be hypersensitive to this drug. Renal impairment, old age and optic neuritis are relative contraindications.

**Adverse events**

Ethambutol produces very few untoward reactions. The incidence of adverse reaction to ethambutol is proportional to the dose and is observed in 15% of patients receiving 50 mg/kg per day, in 5% of patients receiving 25 mg/kg per day, and in 1 to < 2% of patients receiving daily doses of 15 mg/kg (the recommended dose for treatment of tuberculosis). Among the adverse events reported 0.8% experienced diminished visual acuity, 0.5% had a rash, and 0.3% developed drug fever. Adverse effects due to ethambutol are uncommon.
at doses of 15 mg/kg body-weight (Reynolds, 1989). Optic neuritis, resulting in decreased visual acuity and loss of ability to differentiate red from green. Optic neuritis is unknown when ethambutol is given in doses of up to 15 mg/kg body-weight and is rare at doses of up to 25 mg/kg. However, a patient developed rapid progressive deterioration of vision only 3 days after beginning therapy with ethambutol 15 mg/kg body-weight daily by mouth (800 mg) and this patient remained blind over one year after the initial reaction (Karnik et al., 1985).

Subclinical abnormalities of colour discrimination was reported to be relatively common in 54 patients receiving about 15 mg/kg body-weight of ethambutol daily as part of antituberculous chemotherapy when compared with 50 patients receiving other antituberculous agents (Reynolds, 1989).

Peripheral neuropathy has been reported in 3 tubercular patients who had received ethambutol 13 to 50 mg/kg body-weight, among other drugs. It has been reported that a patient who took ethambutol 20 g, rifampicin 9 g and isoniazid 6 g made an uneventful recovery after haemodialysis and treatment with pyridoxine (Reynolds, 1989).

The intensity of the visual impairment is related to the duration of therapy after the decreased visual acuity first becomes apparent and may be unilateral or bilateral. Tests of visual acuity and red-green discrimination prior to the start of therapy and periodically thereafter are thus recommended. Recovery usually occurs when ethambutol is withdrawn; the time required is a function of the degree of visual impairment. (Karnik et al., 1985).

Other side effects that have been observed are pruritus, joint pain, gastrointestinal upset, abdominal pain, malaise, headache, dizziness, mental confusion, disorientation, and possible hallucinations. Numbness and tingling of the fingers owing to peripheral neuritis are infrequent. Anaphylaxis and leukopenia are rare.

Therapy with ethambutol results in an increased concentration of urate in the blood in about 50% of patients, owing to decreased renal excretion of uric acid. The effect may be detectable as early as 24 hours after a single dose or as late as 90 days after treatment is started. This untoward effect is possibly enhanced by isoniazid and pyridoxine (Postlethwaite et al., 1972).
STREPTOMYCIN

Streptomycin is a natural aminoglycoside antibiotic produced by the soil Actinomycete Streptomyces griseus. Streptomycin is used in combination with penicillins for the treatment of bacterial infections in cattle, sheep and pigs. It is also used in agriculture to control bacterial and fungal diseases of selected fruit, vegetables, seed, specialized field crops, ornamental crops, and in ornamental ponds and aquaria to control algae.

Antibacterial Activity

Streptomycin is bactericidal for the tubercle bacillus in vitro. It was noted that, concentrations as low as 0.4 mg/ml may inhibit growth. The vast majority of strains of M. tuberculosis are sensitive to 10 mg/ml. Frequently sensitive strains of mycobacteria is M. kansasii, but other nontuberculous mycobacteria are only occasionally susceptible.

The activity of streptomycin in vivo is essentially suppressive. When the antibiotic is administered to experimental animals prior to inoculation with the tubercle bacillus, they may develop the disease and infection progresses until the animals' immunological mechanisms respond. The presence of viable microorganisms in abscesses and in the regional lymph nodes adds support to the concept that the activity of streptomycin in vivo is to suppress, not to eradicate, the tubercle bacillus. This property of streptomycin may be related to the observation that the drug does not readily enter living cells and thus cannot kill intracellular microbes.

Bacterial Resistance

Because of mutation, large populations of all strains of tubercle bacilli include a number of cells became resistant to streptomycin. However, primary resistance to the antibiotic is found in only 2% to 3% of isolates of M. tuberculosis. Selection for resistant tubercle bacilli occurs in vivo as it does in vitro. Therapy is needed to be continued for longer period for complete eradication of TB, greater the incidence of resistance to streptomycin. When streptomycin was used alone, as many as 80% of patients harbored insensitive tubercle bacilli after 4 months of treatment; many of these microorganisms were not inhibited by concentrations of drug as high as 1 mg/ml.
Absorption Distribution and Excretion

Aminoglycoside antibiotics very poorly cross membranes and about 1% of an oral dose is absorbed, even when there is intestinal inflammation or ulceration (Pratt and Fekaty, 1986).

After oral administration of 600,000 units of streptomycin to a fasted patient, no drug was detected in serum for the following 12 hours when assayed microbiologically using S. aureus. Failure to detect serum levels of the drug could not be attributed to inactivation of the drug by gastric juices, since incubation in gastric juice in vitro at 37°C for 3 hours did not produce any loss of activity (Anderson and Jewell, 1945).

No demonstrable streptomycin in blood after oral administration of 4,000,000 units streptomycin. Only 1% of the dose was recovered in urine and 60%-100% of the drug was recovered unchanged from the faeces (Elias and Durso, 1945; Dollery, 1991).

Streptomycin is poorly absorbed by inhalation, therefore high levels may be produced in respiratory secretions, causing a marked decrease in bacterial flora in the upper respiratory tract (Huber, 1966). The volume of distribution of streptomycin ranged from 30-35% body weight, corresponding to the extracellular fluid volume. (Marshall, 1948).

Approximately 0.5% of the maternal dose of streptomycin was excreted in breast milk in 24 hours; thus, a nursing infant could ingest approximately 5 mg in 24 hours. The recommended therapeutic dose daily for infants is 10-20 mg/kg body weight (Dollery, 1991). After parenteral administration of streptomycin, approximately 50% to 60% of the dose was excreted unchanged in the urine within 24 hours (Anderson and Jewell, 1945).

Renal clearance values for streptomycin ranged from 30-80 ml plasma/minute in humans after i.v. infusion of 10-20 mg/kg body weight in 100 ml saline over 10 minutes (Marshall, 1948). A small amount of reabsorption occurs at the proximal tubules (Pratt and Fekaty, 1986).
Approximately 20% of a parenteral dose of streptomycin could not be accounted for in urine, but no metabolites have yet been identified. Approximately 1% was excreted in bile (Dollery, 1991).

The excretion rate for aminoglycosides after parenteral administration is dependent on renal function and is linearly related to the creatinine clearance rate. The elimination half-life in adults is 2 hours, but 5-6 hours in neonates due to their lower glomerular filtration rate. The aminoglycosides are reported not to be metabolized in humans and are excreted in their active forms by glomerular filtration (Pratt and Fekaty, 1986).

**Adverse Events**

Untoward effects of streptomycin are considered. In one series of 515 patients with tuberculosis who were treated with streptomycin, 8.2% had adverse reactions; half of these involved the auditory and vestibular functions of the eighth cranial nerve. Other relatively frequent problems included rash (in 2%) and fever (in 1.4%). The incidence of congenital malformations in newborns was examined in 1619 mothers who had received treatment for tuberculosis with streptomycin, hydrazide and p-amino salicylic acid. The incidence of congenital malformations was 2.34% in tuberculosis infected subjects. (Marynowski and Sianozecka, 1972).

Ototoxicity is more likely to occur in patients with persistently elevated concentrations of drug in plasma and is linked to mutations in a mitochondrial ribosomal RNA gene, indicating that a gene is one of the factors for this side effect (Bates, 2003). Oxidant stress probably plays a role, and ras activation has been implicated (Battaglia et al., 2003). Ototoxicity is largely irreversible and results from progressive destruction of vestibular or cochlear sensory cells, which are highly sensitive to damage by aminoglycosides (Brummett, 1983). The biochemical mechanism for ototoxicity is poorly understood. Early changes induced by aminoglycosides have been shown in experimental ototoxicity to be reversible by Ca\(^{2+}\). Once sensory cells are lost, however, regeneration does not occur; retrograde degeneration of the auditory nerve follows, resulting in irreversible hearing loss. It has been suggested that aminoglycosides interfere with the active transport system essential for the maintenance of the ionic balance of the endolymph (Neu and Bendush, 1976). Streptomycin produces predominantly vestibular effects.
The incidence of ototoxicity is extremely difficult to determine. Data from audiometry suggest that the incidence may be as high as 25% (Moore et al., 1984a; de Jager and van Altena, 2002).

The incidence of vestibular toxicity is particularly high in patients receiving streptomycin; nearly 20% of individuals who received 500 mg twice daily for 4 weeks for enterococcal endocarditis developed clinically detectable irreversible vestibular damage (Wilson et al., 1984). Since the initial symptoms may be reversible, it is recommended that patients receiving high doses and/or prolonged courses of aminoglycosides be monitored carefully for ototoxicity; however, deafness may occur several weeks after therapy is discontinued.

**Clinical Symptoms of Cochlear Toxicity**

A high-pitched tinnitus often is the first symptom of toxicity. If the drug is not discontinued, auditory impairment may develop after a few days. The tinnitus may persist for several days to 2 weeks after therapy is stopped. Since perception of sound in the high-frequency range (outside the conversational range) is lost first, the affected individual is not always aware of the difficulty, and it will not be detected unless careful audiometric examination is carried out. If the hearing loss progresses, the lower sound ranges are affected, and conversation becomes difficult.

**Clinical Symptoms of Vestibular Toxicity**

Moderately intense headache lasting 1 or 2 days may precede the onset of labyrinthine dysfunction. This is followed immediately by an acute stage in which nausea, vomiting, and difficulty with equilibrium develop and persist for 1 to 2 weeks. Prominent symptoms include vertigo in the upright position, inability to perceive termination of movement ("mental past-pointing"), and difficulty in sitting or standing without visual cues. Drifting of the eyes at the end of a movement so that both focusing and reading are difficult, a positive Romberg test, and rarely, pendular trunk movement and spontaneous nystagmus are outstanding signs. The acute stage ends suddenly and is followed by the appearance of manifestations consistent with chronic labyrinthitis, in which, although symptom less while in bed, the patient has difficulty when attempting to walk or make sudden movements; ataxia is the most prominent feature. The chronic phase persists for
approximately 2 months; it is gradually superseded by a compensatory stage in which symptoms are latent and appear only when the eyes are closed. Adaptation to the impairment of labyrinthine function is accomplished by the use of visual cues and deep proprioceptive sensation for determining movement and position. It is more adequate in the young than in the old but may not be sufficient to permit the high degree of coordination required in many special trades. Recovery from this phase may require 12 to 18 months, and most patients have some permanent residual damage. Although there is no specific treatment for the vestibular deficiency, early discontinuation of the drug may permit recovery before irreversible damage of the hair cells.

Nephrotoxicity
On treatment with aminoglycoside for more than several days will develop mild renal impairment in approximately 8% to 26% of patients that is always reversible (Smith et al., 1980). The toxicity results from accumulation and retention of aminoglycoside in the proximal tubular cells (Aronoff et al., 1983; Lietman and Smith, 1983). The initial manifestation of damage at this site is excretion of enzymes of the renal tubular brush border (Patel et al., 1975). After several days, there is a defect in renal concentrating ability, mild proteinuria, and the appearance of hyaline and granular casts. The glomerular filtration rate is reduced after several additional days (Schentag et al., 1979). The nonoliguric phase of renal insufficiency is thought to be due to the effects of aminoglycosides on the distal portion of the nephron with a reduced sensitivity of the collecting-duct epithelium to endogenous antidiuretic hormone (Appel, 1982). While severe acute tubular necrosis may occur rarely, the most common significant finding is a mild rise in plasma creatinine (5 to 20 mg/ml; 40 to 175 mM). Hypokalemia, hypocalcemia, and hypophosphatemia are seen very infrequently. The impairment in renal function is almost always reversible because the proximal tubular cells have the capacity to regenerate.

Several variables appear to influence nephrotoxicity from aminoglycosides. Toxicity correlates with the total amount of drug administered. Consequently, toxicity is more likely to be encountered with longer courses of therapy. Continuous infusion is more nephrotoxic in animals than is intermittent dosing (Powell et al., 1983); constantly elevated concentrations of drug in plasma above a critical level, which is manifest by
elevated trough serum concentrations, correlate with toxicity in human beings (Keating, et al., 1979).

The nephrotoxic potential varies among individual aminoglycosides. The relative toxicity correlates with the concentration of drug found in the renal cortex in experimental animals. Neomycin, which concentrates to the greatest degree, is highly nephrotoxic in human beings and should not be administered systemically. Streptomycin does not concentrate in the renal cortex and is the least nephrotoxic. Most of the controversy has concerned the relative toxicities of gentamicin and tobramycin. Gentamicin is concentrated in the kidney to a greater degree than is tobramycin, but several controlled clinical trials have given different estimates of their relative nephrotoxicities (Smith et al., 1980; Fong et al., 1981; Keys et al., 1981). If differences between the renal toxicity of these two aminoglycosides do exist in human beings, they appear to be slight. Comparative studies with amikacin, sisomicin, and netilmicin are not conclusive. Other drugs, such as amphotericin B, vancomycin, angiotensin-converting enzyme inhibitors, cisplatin, and cyclosporine, may potentiate aminoglycoside-induced nephrotoxicity (Wood et al., 1986). Furosemide enhances the nephrotoxicity of aminoglycosides in rats if there is concurrent fluid depletion (Mitchell et al., 1977). Clinical studies have not proven conclusively that furosemide itself potentiates nephrotoxicity (Lietman and Smith, 1983), but volume depletion and wasting of K⁺ that accompany its use have been incriminated.

Advanced age, liver disease, diabetes mellitus, and septic shock have been suggested as risk factors for the development of nephrotoxicity from aminoglycosides, but data are not convincing (Moore et al., 1984b). Note, however, that renal function in the elderly patient is overestimated by measurement of creatinine concentration in plasma, and overdosing will occur if this value is used as the only guide in this patient population (Baciewicz et al., 2003).

Even though aminoglycosides consistently alter the structure and function of renal proximal tubular cells, these effects usually are reversible. The most important result of this toxicity may be reduced excretion of the drug, which, in turn, predisposes to ototoxicity. Monitoring drug concentrations in plasma is useful, particularly during prolonged and/or high-dose therapy. However, it never has been proven that toxicity can
be prevented by avoiding excessive peak or trough concentrations of aminoglycosides. In fact, experience with once-daily dosing regimens strongly suggests that high peaks (e.g., 25 mg/ml or higher) do not increase toxicity. The biochemical events leading to tubular cell damage and glomerular dysfunction are poorly understood but may involve perturbations of the structure of cellular membranes. Aminoglycosides inhibit various phospholipases, sphingomyelinases and ATPases and they alter the function of mitochondria and ribosomes (Queener et al., 1983; Humes et al., 1984). Because of the ability of cationic aminoglycosides to interact with anionic phospholipids, these drugs may impair the synthesis of membrane-derived autacoids and intracellular second messengers such as prostaglandins, inositol phosphates, and diacylglycerol. Derangements of prostaglandin metabolism may explain the relationship between tubular damage and reduction in glomerular filtration rate. Others have observed morphological changes in glomerular endothelial cells (decreased number of endothelial fenestrations) (Luft and Evan, 1980) and reduction in the glomerular capillary ultrafiltration coefficient in animals receiving aminoglycosides (Baylis et al., 1977).

Ca$^{2+}$ has been shown to inhibit the uptake and binding of aminoglycosides to the renal brush-border luminal membrane *in vitro* and supplementary dietary Ca$^{2+}$ attenuates experimental nephrotoxicity (Bennett et al., 1982). Aminoglycosides eventually are internalized by pinocytosis. Morphologically, there is clear evidence of accumulation of drug in liposomes, a means by which aminoglycosides are trapped, concentrated (up to 50 times the plasma concentration) (Aronoff et al., 1983), and prepared for extrusion into the urine as multilamellar phospholipid structures called *myeloid bodies* (Swan, 1997).

### Neuromuscular Blockade

An unusual toxic reaction of acute neuromuscular blockade and apnea has been attributed to the aminoglycosides. The order of decreasing potency for blockade is neomycin, kanamycin, amikacin, gentamicin, and tobramycin. In humans, neuromuscular blockade generally has occurred after intrapleural or intraperitoneal instillation of large doses of an aminoglycoside; however, the reaction can follow intravenous, intramuscular, and even oral administration of these agents. Most episodes have occurred in association with
anesthesia or the administration of other neuromuscular blocking agents. Patients with myasthenia gravis are particularly susceptible to neuromuscular blockade by aminoglycosides. Aminoglycosides may inhibit prejunctional release of acetylcholine while also reducing postsynaptic sensitivity to the transmitter (Sokoll and Gergis, 1981), but Ca^{2+} can overcome this effect, and the intravenous administration of a calcium salt is the preferred treatment for this toxicity. Inhibitors of acetylcholinesterase (e.g., edrophonium and neostigmine) also have been used with varying degrees of success.

The administration of streptomycin may produce dysfunction of the optic nerve, including scotomas, presenting as enlargement of the blind spot. Among the less common toxic reactions to streptomycin is peripheral neuritis. This may be due either to accidental injection of a nerve during the course of parental therapy or to toxicity involving nerves remote from the site of antibiotic administration. Paresthesia, most commonly perioral but also present in other areas of the face or in the hands, occasionally follows the use of the antibiotic and usually appears within 30 to 60 minutes after injection of the drug. It can persist for several hours.

Other Untoward Effects

In general, the aminoglycosides have little allergenic potential; anaphylaxis and rash are unusual. Rare hypersensitivity reactions including skin rashes, eosinophilia, fever, blood dyscrasias, angioedema, exfoliative dermatitis, stomatitis, and anaphylactic shock have been reported. Parenterally administered aminoglycosides are not associated with pseudomembranous colitis, probably because they do not disrupt the normal anaerobic flora. Other reactions that have been attributed to individual drugs are discussed below.

2.7 ADVERSE DRUG REACTIONS (ADRs)

Definition: According to WHO’s definition an Adverse Drug Reaction (ADR) is “A response to a drug that is noxious and unintended and occurs at doses normally used in human for the prophylaxis, diagnosis, and treatment of disease, or for modification of physiological function” (WHO, 1972).
Seriousness and Severity of ADRs
According to WHO'S definition an Adverse Drug Reaction (ADR) is "A response to a drug that is noxious and unintended and occurs at doses normally used in human for the prophylaxis, diagnosis, and treatment of disease, or for modification of physiological function"

Serious: A serious adverse events (AEs) or reaction in any untoward medical occurrence that at any dose:
- results in death
- requires inpatients hospitalization or prolongation of hospital stay
- results in persistent or significant disability/incapacity
- is life threatening

The term severe is not synonymous with serious. Words "severe" is used to describe the intensity of specific event (as in mild, moderate or severe); the event itself, however, may be relatively minor medical significance (such as sever headache). Seriousness (not severe) which is based on patients/event outcome or action criteria.

Severity: Severity of adverse drug events were graded on a 3-point scale;
- Mild: Awareness of sign and symptom but easily tolerated
- Moderate: Discomfort sufficient to reduce or affect normal daily activity
- Severe: Causes inability to work or adverse drug events s associated with hospitalization, permanent disability or life threatening

Drug-related diseases and deaths are common and are estimated to cost more than $136 billion a year in the United States, which is higher than the total cost of cardiovascular or diabetes care in that country. Adverse drug events (ADEs) account for most of this cost and results in 140,000 deaths annually, an average fatality rate of 360 deaths per day. The national Adverse Drug Event Prevention Study was designed to enhance current understanding of how common ADEs are and why they occur and to develop strategies to prevent them. The study found an overall rate of 6.5 events per 100 hospital admissions; 28% of these events were judged preventable.
In most of the study, a higher % of ADRs were reported in males as compared to females. According to severity scales, ADRs were classified as mild (41%), moderate (40.2%) and severe (18.2%). As expected, polypharmacy had a major influence on the occurrence of ADRs, with a total of (58.0%) ADRs observed in patients receiving ≥ 4 medications concurrently. Conversely (37.7%) ADRs were detected in patients using three or less medicines. The largest number of reports were associated with antihypertensive therapy (40.2%) followed by antidiabetic (25.4%) and antitubercular drugs (20.5%). Amongst the organ systems affected, GI ADRs constituted a major component (24.7%) followed by adverse skin or cutaneous reactions (22.2%). On causality assessment, nearly 29.5% ADRs were considered as probable, 33.6% as possible and 6.6% could not be categorised and were placed under unassessable. The frequency of ADRs associated with different route of administration was oral (n = 110) > parental (n = 11) > topical (n = 1). These types of study will be useful in promotion of rational prescribing and drug use in the hospital. (Sharma et al., 2007).

A total of 31.8% ADRs were reported in the patient age group of 41–50 years, followed by 27.2% in 31–40 years. Adverse drug reactions were classified as Mild (59.1%), moderate (36.4%) and severe (4.5%). Combination therapy was associated with significantly high occurrence (p < 0.05) of ADRs, with a total of (72.7%) as compared to monotherapy (27.3%). Among the organ systems affected, gastrointestinal ADRs constituted a major component (29.2%), followed by cardiovascular complaints (25%). On the causality scale of WHO, (36.3%) ADRs, were classified probable, (50%) possible, (9.1%) unlikely, and (4.5%) could not be categorised (unclassifiable) (Aqil et al., 2006). Honey can be used as an adjuvant with antituberculosis therapy minimizes the adverse drug reactions induced by Anti-TB drugs in AFB positive pulmonary positive tuberculosis patients. (Sharma et al., 2008).
2.8 ADR DUE TO ANTI-TUBERCULOSIS TREATMENT

A major adverse reaction to one of the first-line antituberculosis drugs, which results in discontinuation of that drug, has several implications. There may be considerable morbidity, even mortality, particularly with drug-induced hepatitis. These events may incur substantial additional costs because of added outpatient visits, tests, and in more serious instances hospitalizations. Alternative agents may have greater problems with toxicity, and are often less effective, so that treatment must be prolonged, with attendant challenges to ensure compliance. As a result the risk of treatment failure and relapse are higher (Yee et al., 2003).

The occurrence, risk factors, morbidity, and mortality of adverse events from isoniazid (INH), particularly hepatotoxicity, have been well defined. (Gholami et al., 2006; Li et al., 2007). Adverse reactions to rifampin (RIF) and ethambutol (EMB) have been well documented although causality of these drugs may be less certain because they are seldom used alone. The dermatological manifestations due to pyrazinamide gain attention, because patients may become noncompliant, which is one of the common cause of treatment failure in TB therapy. Upon occurrence, the suspected drug/s should be stopped immediately and the patient should be managed symptomatically. The patients undergoing treatment on an outpatient basis should be counseled for the early recognition of dermatological manifestations. (Khayyam et al., 2010). The incidence of major side effects associated with pyrazinamide (PZA), is somewhat controversial. Authoritative treatment guidelines have stated that “there does not appear to be a significant increase in hepatotoxicity when PZA is added to INH and RIF, based on results from large scale randomized trials”. However, studies of patients treated for active disease, or receiving 2 months of RIF and PZA for latent infection, have reported serious adverse events attributable to PZA. We have estimated the incidence and associated risk factors of serious side effects from firstline antituberculosis drugs among all patients treated for active tuberculosis (TB) at a single center (Yee et al., 2003; Gholami et al., 2006; Li et al., 2007).
2.9 REPORTED STUDIES FROM LITERATURE

Li et al., (2007) conducted a study in the hospital of Ningbo Medical Center, China having Adverse Drug Reaction Advisory Committee which was established in 1997 to identify all suspicions of drug-induced liver disease (DILD) following a structured prospective report form to analyze the outcome of patients with severe DILD associated with jaundice. They found that, 265 patients were diagnosed with DILD and 140 (52.8%) of them were female. Hepatocellular damage was the most common adverse reactions (72.1%), and the incidence of death was high in these patients, as compared to patients with cholestatic/mixed damage (P < 0.05). There was no difference in age of dead and recovered patients and in duration of treatment between the two groups. The serum total bilirubin, direct bilirubin and aspartate transaminase (AST) values were higher in dead patients than in recovered patients. Antitubercular drugs (3.4%) were found to be the primary etiological factor for fatal DILD. Factors associated with the development of hepatic encephalopathy, ascite, jaundice, alcohol abuse and direct bilirubin. They concluded that death occurs in 9.8% of patients with DILD. Chinese herbal medicine stands out as the most common drug for DILD. While antitubercular drugs are found to be the primary etiological factor for fatal DILD, hepatic encephalopathy, ascites, jaundice, alcohol abuse and direct bilirubin levels are associated with the death of DILD patients (Li et al., 2007)

Gholami et al., (2006) conducted a study to assess the rate of Adverse Drug Reactions (ADRs) induced by Anti-TB drugs in the infectious disease department for a period of one year. To detect serious and preventable recognized ADRs. They enrolled all patients in the study, admitted to the infectious disease department at Imam tertiary teaching hospital in Iran who received Anti-TB drugs from July 2001 to July 2002. These patients were monitored for ADRs during hospital stay. They found that ADRs were recognized as the major cause of hospital admission and Liver & biliary systems are the most frequent organ system affected by ADRs. Hepatitis was observed leading to death in two patients. They concluded that anti-TB drugs could cause significant adverse effects both in quantity and severity leading to hospitalization, prolonged hospital stay and even death. More attention is needed to prevent these reactions (Gholami et al., 2006).
Smink et al. (2006) conducted a study at Leiden University Medical Centre in Netherlands to evaluate side effect due to antitubercular agents. Hepatotoxicity is a well-known side effect of antituberculosis treatment (ATT). If not recognised in time, drug-induced hepatitis can develop, which may rapidly progress to acute liver failure. They describe two patients with acute hepatic failure caused by ATT, whose pretreatment liver function had been normal. Both patients successfully underwent liver transplantation. Possible risk factors predisposing towards ATT-induced hepatic failure were evaluated, and at least four risk factors were present in these patients. Although available guidelines do not advocate routine monitoring of liver function during ATT unless baseline values are elevated or in the case of pre-existent liver disease, this is nevertheless common practice. Liver function should always be measured in patients who develop symptoms during ATT, and rising liver function parameters should prompt immediate action to prevent the occurrence of liver failure. This report underscores that regular monitoring of liver function parameters and adherence to guidelines is especially important in patients with risk factors for ATT-induced liver disease. An evaluation of chronic viral hepatitis in risk groups before starting ATT could be worthwhile (Smink et al., 2006).

Lee et al. (2005) conducted a retrospective case-control study at Pulmonary and Critical Care Medicine in Korea, to determine whether inactive hepatitis B surface antigen (HBsAg) carriers are at a higher risk of drug-induced hepatotoxicity than control subjects during antituberculosis treatment with standard short-course regimens of isoniazid, rifampin, ethambutol, and/or pyrazinamide. They enrolled 110 newly diagnosed active tuberculosis patients with inactive HBsAg carriers who had been treated with isoniazid, rifampin, ethambutol, and/or pyrazinamide in a tertiary university medical center. They found that the baseline characteristics of the 110 inactive HBsAg carriers were similar to those of the 97 noncarriers. A total of 85% of persons in both groups had received an initial treatment regimen that included pyrazinamide. Thirty-eight inactive HBsAg carriers (35%) and 19 control subjects (20%) exhibited elevated liver enzyme levels during antituberculosis treatment (p = 0.016). Drug-induced hepatotoxicity, which was defined as a liver transaminase level of ≥120 IU/L, occurred more frequently in HBsAg carriers than in control subjects. Isoniazid and rifampin were reintroduced as therapy after
AST/ALT levels returned to baseline values in 10 patients among the 13 patients exhibiting drug-induced hepatotoxicity, and these retrials proved to be successful in 7 patients (5 HBsAg carriers and 2 control subjects). They concluded that tuberculosis treatment in HBsAg-positive and HBeAg-negative inactive carriers could be pursued in the usual manner, using standard short-course regimens of isoniazid, rifampin, ethambutol, and/or pyrazinamide, with the condition that monthly liver function tests are performed (Lee et al., 2005).

Stout et al., (2003) conducted a study at Duke University Medical Center, Durham, North Carolina to evaluate an alternative regimen for the treatment of latent tuberculosis infection is 2 months of rifampin and pyrazinamide, but some patients have died of hepatitis associated with this therapy. One hundred fourteen patients received rifampin/pyrazinamide in Wake County, North Carolina, between December 1999 and May 2002. Seventy-seven patients (67.5%) completed a full 2-month course. Nine patients had a history of viral hepatitis or chronic liver disease. Four of 114 patients developed hepatitis on therapy, and another two had symptoms consistent with hepatitis but did not report for laboratory testing. Rifampin/pyrazinamide was associated with a significantly higher rate of hepatitis than previously described with isoniazid therapy for latent tuberculosis but resulted in a high completion rate. The rifampin/pyrazinamide regimen for latent tuberculosis infection may be useful for high-risk, traditionally nonadherent patient groups, but careful remonitoring for toxicity is required (Stout et al., 2003).

Anitha et al., (2003) reported that the human N-acetylation polymorphism is a genetic trait phenotypically reflected by differences in N-acetyltransferase (NAT) activity with therapeutic agents (rapid and slow acetylation). Acetylation polymorphism arises from the allelic variations in human arylamine N-acetyltransferase 2 gene (NAT2), which results in the production of NAT2 proteins with variable enzyme activity or stability. Certain NAT2 traits may contribute to the occurrence of adverse drug effects and act as susceptibility factors for certain malignancies such as bladder or lung cancer. They reported the results of NAT2 genotyping of ethnic communities in South India. One
hundred and sixty-six unrelated individuals belonging to eight Dravidian ethnic communities of South India, with typical Dravidian features, were genotyped for their acetylation status. Slow acetylators were found to be predominant in these populations, with a frequency of 74%. The allele 6A was found in the highest frequency, while 5B/6A was the most frequent genotype. A novel deletion at 859 site was observed in one of these communities; this heterozygous deletion was linked to a homozygous mutation at 481 site. The predominance of slow acetylator genotypes populations conforms to the results in most other Asian populations, where approximately 60% of the individuals have been genotyped as slow acetylators. Sex specificity for acetylator status varied from population to population.

Yee et al., (2003) conducted a study at McGill University in Canada to evaluate incidences of major adverse reactions to antituberculosis drugs which can cause significant morbidity, and compromise treatment regimens for tuberculosis (TB). Among patients treated for active TB they estimated the incidence, and risk factors, of major side effects from first-line anti-TB drugs. Side effects, resulting in modification or discontinuation of therapy, or hospitalization, were attributed on the basis of resolution after withdrawal, and/or recurrence with rechallenge. They found that Pyrazinamide-associated adverse events were associated with age over 60 years and birthplace in Asia, whereas rifampin-associated adverse events were associated with age over 60 years and human immunodeficiency virus-positive status. They concluded that the incidence of pyrazinamide-induced hepatotoxicity and rash during treatment for active TB was substantially higher than with the other first-line anti-TB drugs, and higher than previously recognized (Yee et al., 2003).

Sharma et al., (2002) suggested that several risk factors are involved for the development of hepatotoxicity due to antituberculosis drugs, but the involvement of genetic factors is not fully established. They had studied the major histocompatibility complex (MHC) class II alleles and clinical risk factors for the development of hepatotoxicity in 346 patients with tuberculosis undergoing antituberculosis treatment at All India Institute of Medical Sciences, North India. They found that patients developed drug-induced
hepatotoxicity (DIH), was comparatively older, had lower pretreatment serum albumin, and a higher frequency of moderately/far advanced disease radiographically than the latter. Further, patients with high alcohol intake had threefold higher odds of developing hepatotoxicity. They concluded that the risk of hepatotoxicity from antituberculosis drugs is influenced by clinical and genetic factors.

Peloquin, (2002) in a review reported that, therapeutic drug monitoring (TDM) is one of the important clinical technique also useful in the tuberculosis (TB) setting, as useful for other conditions. This allows the clinician to make informed decisions regarding the timely adjustment of drug therapy. However, some patients are slow to respond to treatment, have drug-resistant TB, are at risk of drug-drug interactions or have concurrent disease states that significantly complicate the clinical situation. Such patients may benefit from TDM and early interventions may preclude the development of further drug resistance. Multiple blood samples are not possible in the clinical setting due to logistical and financial reasons. Therefore, one typically is limited to one or two sampling time points. When only one sample can be obtained, the 2-hour post-dose concentrations of isoniazid, rifampin, pyrazinamide and ethambutol are usually most informative. Blood samples are promptly centrifuged, and the serum is promptly harvested and frozen. During TB treatment, isoniazid considered to be one of the two most important TB drugs, along with rifampin because it causes the greatest early reduction in organisms. Although isoniazid is highly active against TB, low isoniazid concentrations were associated with poorer clinical and bacteriological outcome. Reports from several earlier trials showed a clear dose-response for rifampin and pyrazinamide, so low concentrations for those two drugs also may correlate with poorer treatment outcomes. Therefore, measure serum concentrations of drugs early in the course of treatment. That way, poor drug absorption can be dealt with in a timely manner. This helps to minimise the time that patients are sputum smear- and culture-positive with multidrug-resistant TB, and may prevent the need for even longer treatment durations. Under such complicated circumstances, TDM often is the best available tool for sorting out these interactions and placing the patient the necessary doses that they require. When TDM combined with clinical and bacteriological
Chapter 2

Review of Literature

data, it can be a decisive tool, allowing the clinician to successfully treat even the most complicated TB patients.

Wobeser et al., (1999) conducted a study to evaluate completion of treatment of active cases of tuberculosis (TB) is the most important priority of TB control programs to assess treatment completion for active cases of pulmonary TB in Toronto. The main outcome analysed was treatment outcome, with cases classified as completed (record of treatment completion noted), transferred (patient transferred to another centre but no treatment results available), defaulted (record of defaulting in patient chart but no record of treatment completion elsewhere, or patient still receiving treatment more than 15 months after diagnosis) or dead (patient died before treatment completion). They concluded that, treatment completion rates in tertiary care hospitals in Toronto in 1992/93 were below the rate recommended by the World Health Organization.

Schaberg et al., (1996) conducted a study to determine the current incidence of side-effects severe enough to cause intolerance of standard antituberculosis therapy with isoniazid, rifampin and pyrazinamide in patients hospitalized as a result of pulmonary tuberculosis. Five hundred and nineteen patients with proven pulmonary tuberculosis, who initially received standard antituberculosis therapy, were retrospectively studied in the department of infectious diseases in a teaching chest hospital. The incidence of severe side-effects related to the therapy, which led to the definitive termination of one of the three standard drugs, was measured and the risk factors for intolerance were analysed. Final termination of either isoniazid, rifampin or pyrazinamide because of severe side-effects was necessary in 121 of the 519 patients (23%). The most severe side-effects leading to final termination of one drug were hepatotoxicity, exanthema, and arthralgia. Pyrazinamide showed more severe side-effects than isoniazid and rifampin. Significant risk factors for intolerance of the standard therapy following a multivariate analysis were a history of hepatitis and an age \( \geq 60 \) yrs. Both of these risk factors were also significantly associated with the intolerance of pyrazinamide but not of isoniazid and rifampin. The concluded that side-effects of standard antituberculosis therapy are

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frequent in hospitalized patients aged ≥60 years or with a history of previous hepatitis, and are probably due to pyrazinamide rather than to isoniazid or rifampin.

Wong et al., (1995) reported in a case study that a 67 year old woman presented with miliary tuberculosis were treated with streptomycin, isoniazid, rifampicin, ethambutol and pyrazinamide. They reported that rifampicin-induced thrombocytopenia after 6 weeks of treatment, and skin rash, blood eosinophilia and pulmonary infiltrates after 8 weeks of therapy. The latter was found to be ethambutol related. Additional evidence, including blood and sputum eosinophilia and the rapidity of its response to corticosteroid, suggested that the pulmonary infiltrates might also be eosinophilic in nature. This was the first report of such adverse drug reaction, induced by ethambutol.

Singhal et al., (1990) conducted a study to find out the incidences of adverse drug reaction to antitubercular drugs. 752 patients of tuberculosis were initiated therapy with 2, 3 or 4 drugs administered simultaneously in various combinations. They found that, Streptomycin induced ADR’s were observed in 50 (14.2%) patients. The commonest ADR encountered was giddiness (1.2%) which was unrelated to number of injections administered, but appears early in higher age group. Isoniazid caused ADRs in 37 (4.9%) patients. Peripheral neuropathy (2.1%) was the most frequent encountered ADR due to INH. 9.1% patients developed ADRs following thiopacitazone administration. Gastric irritation was the commonest ADR (3.5%) followed by hepatotoxicity (1.16%), jaundice (0.19%), skin rash (2.5%), Stevens Johnson syndrome (0.38%) and giddiness (0.5%). Ethambutol was found to be responsible for ADRs in 25 (7.3%) of patients. No impairment of vision was seen. Constriction of vision fields occurred in 5.5% and diminished vision acuity in 2%. With the use of rifampicin, asymptomatic elevation of liver enzyme was observed in 6.85% and jaundice in 5.7% of the 175 patients treated with drug. They concluded that toxicity of streptomycin increased with age and was not related to sex or duration of the therapy. Reactions to isoniazid, ethambutol and thiacetazone were not related to age, sex and duration of therapy. However the incidences of ADR were marginally higher among females following rifampicin (Singhal et al., 1990).
Zysset et al., (1986) conducted a study to see the influence of concomitant administration of isoniazid (INH) on the acetylation of sulphadimidine in 6 healthy volunteers, previously identified as having the fast acetylator phenotype. INH was administered in a slow release form (500 mg tablet) 1 hour before the sulphadimidine. Acetylation of sulphadimidine was measured in plasma 6 h after its intake and in urine collected between 5 and 6 hours. INH significantly decreased the acetylated fraction of sulphadimidine in plasma from 69.0 to 54.0 and in urine from 85.9 to 81.2%. This was reflected in a significantly higher plasma concentration of unconjugated sulphadimidine and reduced urinary excretion of acetylated sulphadimidine.

Gupta et al. (1984) conducted a study to determined isoniazid acetylation phenotypes in 110 patients by sulphadimidine acetylation test. Appearance of more than 65% of acetylated sulphadimidine in urine at 6th hours were classified as fast acetylators, those with less than 50% as slow acetylators and others with values between 50-65% as intermediate acetylators. They found that, 39.09% patients were fast, 46.36% intermediate and 14.55% slow acetylators. Sulphadimidine acetylation showed no variation due to presence of disease, age, sex, religion, place of origin, height, weight and smoking habits.

Bouayad et al., (1982) was conducted a preliminary study to determine the acetylator phenotype for isoniazid for the first time on 100 patients. A correlation was shown between the blood and urinary methods; 59% were rapid acetylators and 41% slow acetylators, which were similar levels to those found in African. The predominance of rapid acetylators certainly explains the excellent tolerance of the high dose of INH.
### Table 4: Reported Adverse Drug Reaction due to Anti-tuberculosis Therapy

#### ISONIAZID (INH)

<table>
<thead>
<tr>
<th>NAME OF THE COUNTRY</th>
<th>ADVERSE REACTIONS (%)</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>Peripheral neuritis (2.1%)</td>
<td>Singhal et al., (1990)</td>
</tr>
<tr>
<td>Turkey</td>
<td>Psychiatric changes (0.7%)</td>
<td>Gulbay et al., (2006)</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuritis (0.1%)</td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>Hepatitis (2%)</td>
<td>Yee et al., (2003)</td>
</tr>
<tr>
<td></td>
<td>Rash (1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GI (1%)</td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>Hepatotoxicity (4%)</td>
<td>Schaberg et al., (1996)</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuritis (1.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exanthema (1.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arthralgia (0.2%)</td>
<td></td>
</tr>
<tr>
<td>Iran</td>
<td>Constipation (17.3%)</td>
<td>Gholami et al., (2006)</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuritis (6.2%)</td>
<td></td>
</tr>
<tr>
<td>East Carolina University</td>
<td>Hepatotoxicity (4%)</td>
<td>McNeill et al., (2003)</td>
</tr>
</tbody>
</table>

#### STREPTOMYCIN (SM)

<table>
<thead>
<tr>
<th>NAME OF THE COUNTRY</th>
<th>ADVERSE REACTIONS (%)</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>Giddiness (12%)</td>
<td>Singhal et al., (1990)</td>
</tr>
<tr>
<td>Turkey</td>
<td>Ototoxicity (1.7%)</td>
<td>Gulbay et al., (2006)</td>
</tr>
<tr>
<td></td>
<td>Cutaneous reaction (0.2%)</td>
<td></td>
</tr>
</tbody>
</table>
### RIFAMPICIN (RIF)

<table>
<thead>
<tr>
<th>NAME OF THE COUNTRY</th>
<th>ADVERSE REACTIONS (%)</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turkey</td>
<td>Hepatotoxicity (0.2%)</td>
<td>Gulbay et al., (2006)</td>
</tr>
<tr>
<td></td>
<td>Flu-like syndrome (0.26%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cutaneous reaction (0.1%)</td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>Rash (2%)</td>
<td>Yee et al., (2003)</td>
</tr>
<tr>
<td></td>
<td>GI (1%)</td>
<td></td>
</tr>
<tr>
<td>India</td>
<td>Hepatic impairment (12.5%)</td>
<td>Singhal et al., (1990)</td>
</tr>
<tr>
<td></td>
<td>Jaundice (5.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gastric irritation (1.7%)</td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>Hepatotoxicity (1.5%)</td>
<td>Schaberg et al., (1996)</td>
</tr>
<tr>
<td>Iran</td>
<td>Headache (8.7%)</td>
<td>Gholami et al., (2006)</td>
</tr>
<tr>
<td></td>
<td>Rash &amp; pruritis (4.9%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diarrhea (3.7%)</td>
<td></td>
</tr>
</tbody>
</table>

### ETHAMBUTOL (EMB)

<table>
<thead>
<tr>
<th>NAME OF THE COUNTRY</th>
<th>ADVERSE DRUG REACTIONS (%)</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turkey</td>
<td>Change in visual acuity (0.1%)</td>
<td>Gulbay et al., (2006)</td>
</tr>
<tr>
<td>India</td>
<td>Constriction in visual field (5.5%)</td>
<td>Singhal et al., (1990)</td>
</tr>
<tr>
<td></td>
<td>Diminished visual acuity (2.1%)</td>
<td></td>
</tr>
<tr>
<td>Iran</td>
<td>Burning eye &amp; Blurred vision (2.4%)</td>
<td>Gholami et al., (2006)</td>
</tr>
<tr>
<td>Canada</td>
<td>Visual (1%)</td>
<td>Yee et al., (2003)</td>
</tr>
</tbody>
</table>
## PYRAZINAMIDE (PYZ)

<table>
<thead>
<tr>
<th>NAME OF THE COUNTRY</th>
<th>ADVERSE DRUG REACTIONS (%)</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>Gastric irritation and blood in vomiting</td>
<td>Singhal et al., (1990)</td>
</tr>
<tr>
<td>Germany</td>
<td>Hepatotoxicity (5%)</td>
<td>Schaberg et al., (1996)</td>
</tr>
<tr>
<td></td>
<td>Exanthema (5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arthralgia (2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other (1.4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nausea (0.9%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperurecemia (0.6%)</td>
<td></td>
</tr>
<tr>
<td>Turkey</td>
<td>Hepatotoxicity (0.6%)</td>
<td>Gulbay et al., (2006)</td>
</tr>
<tr>
<td></td>
<td>Hyperurecemia (0.6%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fever (0.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cutaneous reaction (0.1%)</td>
<td></td>
</tr>
<tr>
<td>Nepal</td>
<td>Maculopapular Rash</td>
<td>Kishore et al., (2007)</td>
</tr>
<tr>
<td>East Carolina University</td>
<td>Hepatotoxicity (13%)</td>
<td>McNeill et al., (2003)</td>
</tr>
<tr>
<td>Canada</td>
<td>Hepatitis (2%)</td>
<td>Yee et al., (2003)</td>
</tr>
<tr>
<td></td>
<td>Rash (2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GI (1%)</td>
<td></td>
</tr>
</tbody>
</table>