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ORIGINAL ARTICLE

# Adverse reactions among patients being treated for multi-drug resistant tuberculosis at Abbassia Chest Hospital

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**KEYWORDS**

Multi-drug resistant tuberculosis;
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**Abstract** *Background:* Pulmonary tuberculosis is a major cause of morbidity and mortality worldwide, resulting in the greatest number of deaths due to any one single infectious agent. Drug resistance threatens global tuberculosis control efforts.

*Objective:* The aim of this study was to assess adverse reactions of second-line TB drugs in patients treated for MDR-TB at Abbassia Chest Hospital from 1st of January 2009 to 1st of January 2012.

*Subjects and methods:* This study included 107 patients admitted at Abbassia Chest Hospital; during the period from January 2009 to January 2012. The patients were resistant to at least Rifampicin and INH. All patients' files were analyzed and the following data were discussed: meticulous history taking, complete clinical examination, drug susceptibility testing, and initial laboratory investigations, adverse reactions were determined by clinical criteria and/or laboratory data, severity code, management of side effects and fate of treatment.

*Results:* 72.9% of the patients were males and 27.1% were females. The mean of age was 37.1 years. The special habits detected among the studied cases were tobacco smoking, drug addiction and alcohol intake. According to type of resistance, acquired resistance was 95.3% and primary resistance was 4.7%. The most common co-morbidities associated with MDR-TB in the studied cases were diabetes (29.9%) and chronic obstructive lung disease (11.2%). Side effects of drugs were; 57% GIT manifestations, 53.3% peripheral neuritis, hypokalemia 26.2%, irritable bowel syndrome 22.4%, ototoxicity 17.8%, skin reaction 10.3%, hypothyroidism 10.3%, hepatotoxicity 9.3%, hypoalbuminemia 5.6%, depression 3.7%, arthritis 0.9%, gynecomastia 2.8%,

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hyponatremia 5.6%, hypomagnesaemia 1.9%, dizziness 0.9%, nephrotoxicity 3.7%. Most of the drugs' side effects started to appear within the first 3 months of treatment. The frequency of nephrotoxicity, hepatotoxicity and hypoalbuminemia were significantly higher in diabetic than in non-diabetic cases. Elevations of liver enzymes began from the 3rd month after treatment and these elevations became statistically significant beginning from the 6th month. Also, elevations of creatinine levels began from the 3rd month after treatment and became statistically significant beginning from the 6th month, while there were no significant changes in potassium levels among the studied cases all through the follow up period. It was noticed that highly significant gain of body weight started from the 3rd month after treatment. 92.5% of the studied cases were cured, 6.5% died and 0.9% was defaulter. The predictors of patients' outcome were sputum conversion, number of previous TB treatment and associated co-morbidities.

*Conclusions:* There is a relation between both tobacco smoking and drug addiction, and MDR TB. The most common type of resistance is acquired resistance because of lack of adherence to treatment or inappropriate treatment. The most common co-morbidities associated with MDR TB are diabetes and chronic obstructive lung diseases. The most important predictors of patients' outcome are sputum conversion, number of previous TB treatment and presence of co-morbidities.



## Introduction

Tuberculosis (TB) is an infectious bacterial disease caused by *Mycobacterium tuberculosis*, which most commonly affects the lungs. It is transmitted from person to person via droplets from the throat and lungs of people with the active respiratory disease [1].

Approximately 9.4 million new cases and 1.7 million deaths were encountered per year worldwide [2].

Morbidity and mortality are especially high in specific populations such as those with underlying immunosuppression or very young children [3].

Tuberculosis remains a public health problem in Egypt. Although Egypt is in the era of epidemiological transition from communicable to non-communicable diseases like many other countries, TB, still, must be addressed and handled as a health problem affecting large sectors in the society, especially the poor and the vulnerable [4].

Early diagnosis and immediate initiation of treatment are essential for an effective TB control program. Delay in diagnosis is significant to both disease prognosis at the individual level and transmission within the community. Most transmissions occur between the onset of cough and initiation of treatment. The diagnosis of pulmonary TB depends on clinical suspicion, response to treatment, chest radiographs, staining for acid fast bacilli (AFB), culture for TB, and, nucleic acid amplification (NAA) assays [5].

The most effective anti-TB drugs are Isoniazid (INH) and Rifampicin (RIF). Resistant Mycobacteria to at least one of these drugs are the cause of Multidrug-resistant tuberculosis (MDR-TB). This type of resistance is highly problematic due to limited sources of drugs as well as the high toxicity, low efficacy and high cost of second-line tuberculosis drugs [6].

Multidrug-resistant TB (MDR-TB) is caused by bacteria that are resistant to at least Isoniazid and Rifampicin, the most effective anti-TB drugs. MDR-TB results from either primary infection with resistant bacteria or may develop in the course of a patient's treatment [7].

In 2008, an estimated 390,000–510,000 case of MDR-TB emerged globally. Among TB cases, 3.6% are estimated to have MDR-TB. Twenty-two of 48 African countries reported first-line TB drug resistance, the estimated number of MDR-TB cases (primary and acquired) in 2008 was 69,000 (53,000–110,000). Although the rate of drug resistance is continuously increasing, only around 7% of estimated cases are detected. The control of drug resistant disease is difficult especially in high burden countries due to poor laboratory services and the slow nature of conventional drug susceptibility testing [8].

In Egypt, a nationwide drug resistance survey was carried out in 2002, in which a total number of 849 patients enrolled, 632 new and 217 old patients [4].

There are several ways that drug resistance to TB and drug resistance in general, can be prevented:

- Rapid diagnosis and treatment of TB.
- Completion of treatment.
- Patients with HIV/AIDS should be identified and diagnosed as soon as possible.
- Identify contacts who could have contracted TB: i.e. family members, people in close contact, etc.
- Research: Much research and funding is needed in the diagnosis, prevention and treatment of TB and MDR TB [9,10].

The emergence of multidrug resistant TB (MDR-TB), i.e. which is resistant to at least Isoniazid (INH) and Rifampicin (RIF), is of great concern, because it requires the use of second-line drugs that are difficult to procure and are much more toxic and expensive than FLDs [11].

Laboratory monitoring is required for patients receiving a regimen with second-line anti-TB drugs. Adverse effects can be occult (not obviously noted by taking the history of the patient or by physical examination). Note the following important aspects of laboratory monitoring for adverse effects:

- Renal toxicity monitoring
- Electrolyte monitoring
- Monitoring for hypothyroidism
- Monitoring liver toxicity
- Pregnancy testing
- Audiometry [12].

**Subjects and methods**

This was a retrospective study, that included (107) MDR patients admitted at Abbassia Chest Hospital between 1st January 2009 and 1st January 2012.

- Inclusion criteria:
  - ✓ All patients included in this study were diagnosed in the same year as MDR.
  - ✓ They were resistant to at least Rifampicin and INH.

- Exclusion criteria:
  - ✓ MDR patients readmitted after discharge.

All patients' files were analyzed and the following data were discussed:

- Meticulous history taking with special attention to:
  - ✓ Whether primary or secondary resistance.
  - ✓ History of second-line TB drugs.
  - ✓ Patient's compliance and follow up of treatment.
  - ✓ History of HIV infection.

- Complete clinical examination.
- Drug Susceptibility testing:

Susceptibility was performed by conventional Drug Incorporation Method, using 4 anti-tuberculous agents: Isoniazid, Streptomycin, Rifampicin and Ethambutol.

- The initial laboratory investigations:
  - Sputum examination:
    - ✓ Direct smear examination using Ziehl–Nielsen stain.
  - Drug susceptibility tests for first-line anti-TB drugs.
  - Complete blood count (CBC).
  - ESR.
  - Fasting and two hours post prandial blood sugar.
  - Serum sodium and potassium on admission then on demand.
  - Liver functions:
    - ✓ Total serum bilirubin.
    - ✓ SGPT and SGOT.
    - ✓ Serum albumin, total serum protein and A/G ratio.
  - Renal functions:
    - ✓ Serum creatinine
  - HIV testing.

- The patient received the following regimen, if proved to be MDR-TB:
- Regimen (1): Kanamycin, Ethionamide, Cycloserine, PAS, Ofloxacin.
- Regimen (2): Amikacin, Ethionamide, Cycloserine, PAS, Ofloxacin.
- Regimen (3): Capreomycin, Ethionamide, Cycloserine, PAS, Ofloxacin.
- Regimen (4): Streptomycin, Ethionamide, Cycloserine, PAS, Ofloxacin.
- Ethambutol + Ethionamide, Cycloserine, PAS, Ofloxacin + one of the injectable drugs.
- Adverse reactions were determined by clinical criteria and/or laboratory data such as:
  - ✓ Sputum smears and culture; monthly until conversion, then smears monthly and culture quarterly.
  - ✓ Chest X-ray every 6 months.
  - ✓ Serum creatinine, monthly while receiving injectable drugs.
  - ✓ Serum potassium and sodium; monthly while receiving injectable drugs.
  - ✓ Liver enzymes; periodic monitoring (every 1–3 months).
  - ✓ Thyroid stimulating hormone (TSH) every 6 months if receiving Ethionamide or Para amino-salicylic acid and monthly for signs and symptoms of hypothyroidism.
  - ✓ Audiometry, visual acuity and color vision evaluation, psychiatric disorders assessment, hematological changes and allergic reactions when indicated.

- Side effects of 2nd line treatment:
  - ✓ Ototoxicity.
  - ✓ Psychiatric disorders.
  - ✓ Gastrointestinal effects.
  - ✓ Arthralgia, arthritis.
  - ✓ Central nervous system (CNS): seizures.
  - ✓ Hepatotoxicity.
  - ✓ Dermatological.
  - ✓ Leucopenia.
  - ✓ Peripheral neuropathy.
  - ✓ Nephrotoxicity.
  - ✓ Hypothyroidism.

- Severity code:
  - ✓ Asymptomatic.
  - ✓ Does not affect daily activities.
  - ✓ Limits daily activities.
  - ✓ Life threatening hospitalization.

- Management of side effects:
  - ✓ Reduced Dosage of Suspected Drug(s).
  - ✓ Removal of Drug(s) from the Regimen.
  - ✓ Specific treatment for every adverse reaction.

- Fate of treatment:
  - ✓ Cured.
  - ✓ Defaulter.
  - ✓ Treatment failure and begin re-treatment course.
  - ✓ Died.

*Statistical methods*

- ✓ The collected data were coded, tabulated, and statistically analyzed using SPSS Program (Statistical Package for Social Sciences) software version 18.0.
- ✓ Descriptive statistics were done for quantitative parametric data as minimum and maximum of the range as well as mean ± SD (standard deviation) for numerical parametric and median and 1st and 3rd inter-quartile range for numerical non parametric, while they were done for qualitative data as number and percentage.

- ✓ Inferential analyses were done for quantitative variables using paired *t*-test in cases of two dependent groups with parametric data and Wilcoxon signed rank test in cases of two dependent groups with non-parametric data. In qualitative data, inferential analyses for independent variables were done using Chi square test for differences between proportions.
- ✓ The level of significance was taken at *P* value $< 0.050$ is significant, otherwise is non-significant. The *P*-value is a statistical measure for the probability that the results observed in a study could have occurred by chance.

## Results

Table 1 shows that follow up data were available for 107 patients, while only 26 patients completed one year of follow up data.

The mean age of the studied cases was 37.1 years, males represented 72.9% of the cases and females represented 27.1%. Table 2 also shows the frequency of associated special habits among the studied cases (smoking 27.1%, addiction 5.6%, alcohol 3.7%).

Table 3 shows that 49.6% of the patients had co-morbidities {29.9% of them were diabetic, 3.7% had chronic liver disease, 11.2% had COPD and only one patient was HIV positive}.

Table 4 shows that 102 patients were 2ry resistant and five patients were 1ry resistant to anti TB drugs.

Table 5 shows the 2nd line drugs prescribed to the patients, in which all of them shared 4 drugs (Ethionamide – Cycloserine – PAS – Ofloxacin), but they differed as regards the injectable drugs (Kanamycin 53 – Amikacin 33 – Capreomycin 14 – Streptomycin 7 – Ethambutol 22).

**Table 1** Available follow up data of the studied cases.

| Month | No. |
|---|---|
| 1st month | 107 |
| 3rd month | 104 |
| 6th month | 89 |
| 9th month | 49 |
| 12th month | 26 |

**Table 2** Demographic and special habits of the studied cases.

| | Mean ± SD | Range |
|---|---|---|
| Age (years) | 37.1 ± 11.9 | 15.0–67.0 |
| | *N* | % |
| Sex | | |
| Female | 29 | 27.1 |
| Male | 78 | 72.9 |
| Smoking | 29 | 27.1 |
| Addiction | 6 | 5.6 |
| Alcohol | 4 | 3.7 |

*N* = 107.

**Table 3** Co-morbidities among the studied cases.

| Co-morbidities | No. | % |
|---|---|---|
| DM | 32 | 29.9 |
| Chronic liver disease | 4 | 3.7 |
| Chronic renal disease | 1 | 0.9 |
| Ischemic heart disease | 2 | 1.9 |
| Chronic pulmonary disease | 12 | 11.2 |
| HIV | 1 | 0.9 |
| No co-morbidities | 55 | 51.4 |

*N* = 107.

**Table 4** Types of resistance among the studied cases.

| | *N* | % |
|---|---|---|
| Resistance | 5 | 4.7 |
| • 1ry | 102 | 95.3 |
| • 2ry | | |

*N* = 107.

Table 6 shows the different anti TB regimens prescribed to the studied cases.

Table 7 shows that the majority of cases cured after treatment (99 patients), one patient was defaulter and only seven patients died.

Table 8 and Fig. 1 show that the elevations of SGPT began from the 3rd month after starting treatment and these

**Table 5** Anti-tuberculous drugs used among the studied cases.

| Drugs | *N* | % |
|---|---|---|
| Ethionamide | 107 | 100.0 |
| Cycloserine | 107 | 100.0 |
| PAS | 107 | 100.0 |
| Ofloxacin | 107 | 100.0 |
| Kanamycin | 53 | 49.5 |
| Amikacin | 33 | 30.8 |
| Ethambutol | 22 | 20.6 |
| Capreomycin | 14 | 13.1 |
| Streptomycin | 7 | 6.5 |

*N* = 107.

**Table 6** Anti-tuberculous Regimens used among the studied cases.

| | *N* | % |
|---|---|---|
| Regimen (1) Kanamycin, Ethionamide, Cycloserine, PAS, Ofloxacin | 53 | 49.5 |
| Regimen (2) Amikacin, Ethionamide, Cycloserine, PAS, Ofloxacin | 33 | 30.8 |
| Regimen (3) Capreomycin, Ethionamide, Cycloserine, PAS, Ofloxacin | 14 | 13.1 |
| Regimen (4) Streptomycin, Ethionamide, Cycloserine, PAS, Ofloxacin | 7 | 6.5 |
| Ethambutol + Ethionamide, Cycloserine, PAS, Ofloxacin + one of injectable drugs | 22 | 20.6 |

*N* = 107.

elevations became statistically significant beginning from the 6th month.

Table 9 and Fig. 2 show that elevations of creatinine level began from the 3rd month after starting treatment and became statistically significant beginning from the 6th month.

Table 10 and Fig. 3 show that there were no significant changes in potassium levels among the studied cases all through the follow up period.

Table 11 and Fig. 4 show that highly significant gain of body weight started from the 3rd month after the beginning of the treatment.

Table 12 and Fig. 5 show that GIT manifestations was the most frequent side effect, followed by PN, Hypokalemia, IBS, ototoxicity, Hypothyroidism, Skin manifestations, Hepatotoxicity and nephrotoxicity.

**Table 7** Outcome of the studied cases.

| | No. | % |
|---|---|---|
| Negative sputum | 99 | 92.5 |
| Treatment default | 1 | 0.9 |
| Died | 7 | 6.5 |

**Table 8** SGPT (IU/L) among the studied cases.

| Month | No. | Median (IQR) | Range | #P |
|---|---|---|---|---|
| 1st month | 107 | 15.0 (12.0–22.0) | 0.7–164.0 | |
| 3rd month | 104 | 16.0 (14.0–22.0) | 0.6–181.0 | 0.252 |
| 6th month | 89 | 18.0 (15.0–23.0) | 0.7–91.0 | 0.049* |
| 9th month | 49 | 18.0 (15.0–24.0) | 0.9–226.0 | 0.050* |
| 12th month | 26 | 21.5 (14.0–30.3) | 12.0–330.0 | 0.019* |

IQR: Interquartile range.
# Wilcoxon signed rank test, difference from each month to 1st month.
* Significant.

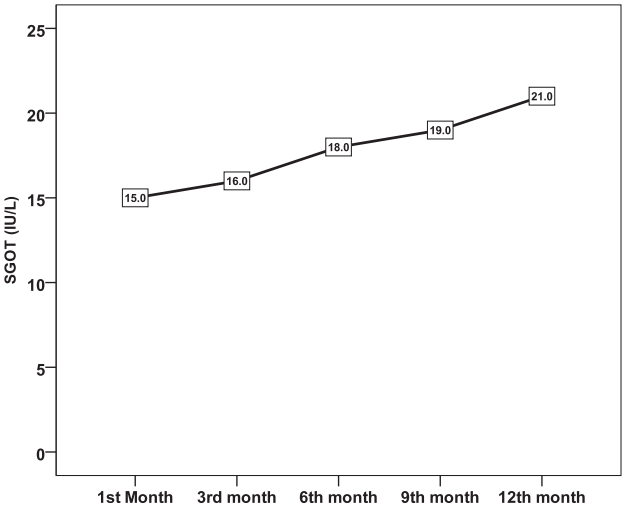


**Figure 1** SGPT among the studied cases.

**Table 9** Creatinine (mg/dL) among the studied cases.

| Month | No. | Mean ± SD | Range | #P |
|---|---|---|---|---|
| 1st month | 107 | 0.88 ± 0.20 | 0.60–2.10 | |
| 3rd month | 104 | 0.91 ± 0.33 | 0.60–3.30 | 0.434 |
| 6th month | 89 | 0.95 ± 0.34 | 0.60–2.80 | 0.047* |
| 9th month | 49 | 0.96 ± 0.27 | 0.50–1.90 | 0.006* |
| 12th month | 26 | 0.95 ± 0.28 | 0.60–2.00 | 0.049* |

# Paired *t*-test, difference from each month to 1st month.
* Significant.

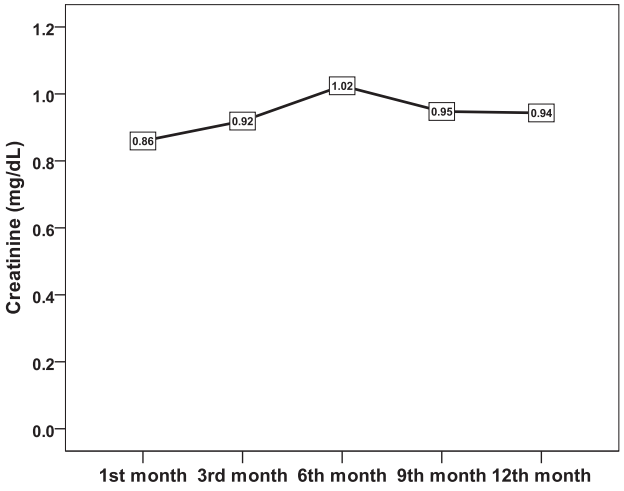


**Figure 2** Creatinine among the studied cases.

**Table 10** Potassium (mmol/L) among the studied cases.

| Month | No. | Mean ± SD | Range | #P |
|---|---|---|---|---|
| 1st month | 107 | 4.05 ± 0.40 | 3.10–5.50 | |
| 3rd month | 104 | 4.04 ± 0.54 | 2.70–6.10 | 0.958 |
| 6th month | 89 | 4.10 ± 0.48 | 2.40–5.20 | 0.450 |
| 9th month | 49 | 4.06 ± 0.55 | 2.60–5.80 | 0.938 |
| 12th month | 26 | 4.08 ± 0.45 | 3.40–5.00 | 0.223 |

# Paired *t*-test, difference from each month to 1st month.

Table 13 shows the severity of adverse reactions; (1) Asymptomatic, (2) Does not affect daily activities, (3) Limits daily activities.

Table 14 shows that most of the drugs' side effects started to appear within the first 3 months after starting treatment.

Table 15 and Fig. 6 show that there was no significant relation between Kanamycin and ototoxicity.

Table 16 and Fig. 7 show that there was no significant relation between Amikacin and Streptomycin, and hypokalemia.

Table 17 and Fig. 8 show that there was no significant relation between Streptomycin and IBS.

Table 18 and Fig. 9 show that there was no significant relation between Amikacin and Streptomycin, and hepatotoxicity.

Table 19 and Fig. 10 show that there was significant relation between Kanamycin and hypothyroidism.

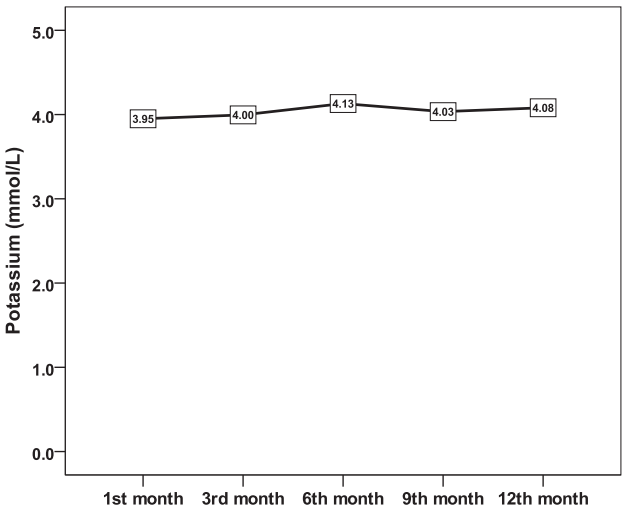


**Figure 3** Potassium among the studied cases.

**Table 11** Weight gain (kg) among the studied cases.

| Month | No. | Mean ± SD | Range | #P |
|---|---|---|---|---|
| 1st month | 107 | 59.9 ± 13.0 | 37.0–110.0 | |
| 3rd month | 104 | 61.2 ± 13.0 | 35.0–111.0 | <0.001* |
| 6th month | 89 | 63.4 ± 13.1 | 38.0–112.0 | <0.001* |
| 9th month | 49 | 65.7 ± 14.3 | 38.0–114.0 | <0.001* |
| 12th month | 26 | 67.2 ± 15.2 | 40.0–107.0 | <0.001* |

# Paired *t*-test, difference from each month to 1st month.
* Significant.

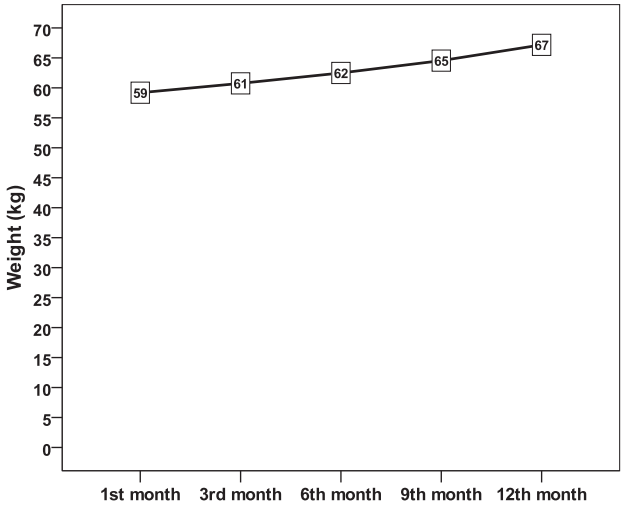


**Figure 4** Weight gain among the studied cases.

Table 20 and Fig. 11 show that there was no significant relation between Kanamycin and GIT manifestations.

Table 21 and Fig. 12 show that there was no significant relation between Kanamycin and PN.

Table 22 and Figs. 13 and 14 show that: PN was significantly highest in Kanamycin regimen and least in Capreomycin regimen. IBS was significantly highest in Streptomycin regimen and least in Capreomycin regimen.

**Table 12** Drugs' side effects among the studied cases.

| Side effects | No. | % |
|---|---|---|
| Ototoxicity | 19 | 17.8 |
| Nephrotoxicity | 4 | 3.7 |
| Dizziness | 1 | 0.9 |
| Hypokalemia | 28 | 26.2 |
| Hypomagnesaemia | 2 | 1.9 |
| Hyponatremia | 1 | 0.9 |
| IBS | 24 | 22.4 |
| Hepatotoxicity | 10 | 9.3 |
| Gynecomastia | 3 | 2.8 |
| Hypothyroidism | 11 | 10.3 |
| Arthritis | 1 | 0.9 |
| GIT manifestations | 59 | 57 |
| PN | 57 | 53.3 |
| Hypoalbuminemia | 6 | 5.6 |
| Skin | 11 | 10.3 |
| Depression | 4 | 3.7 |

$N = 107$.

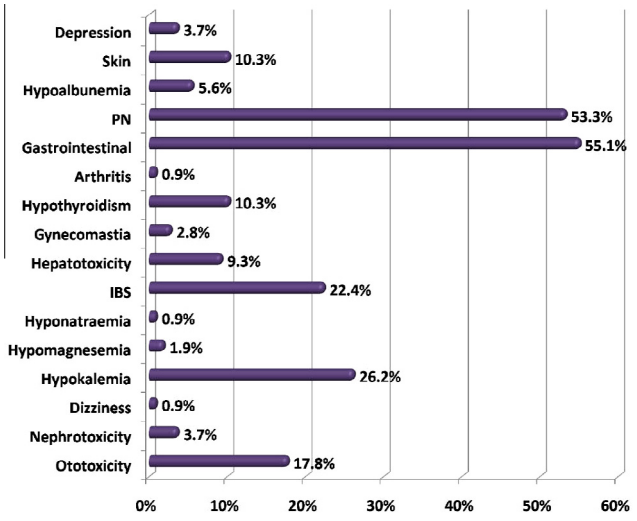


**Figure 5** Drugs' side effects among the studied cases.

Table 23 and Fig. 15 show that the frequency of Nephrotoxicity, Hepatotoxicity and Hypoalbuminemia was significantly higher in diabetic than in non-diabetic cases.

## Discussion

Multi drug resistant tuberculosis (MDR-TB) is a growing hazard to human health worldwide. MDR-TB is suspected if sputum is persistently positive for acid fast bacilli with clinical and radiological deterioration after multiple courses of irregular/regular treatment. MDR tuberculosis is defined as disease due to M tuberculosis that is resistant to Isoniazid (H) and Rifampicin (R), with or without resistance to other drugs[3]. Primary drug resistance is defined as drug resistance in a patient who has not received any anti-tubercular treatment in the past, while acquired drug resistance is defined as resistance that develops in a patient who has received prior chemotherapy [13].

**Table 13** Side effect severity among the studied cases.

| Side effects | Severity | No. | % |
|---|---|---|---|
| Ototoxicity | 1 | 8 | 42.1 |
| | 2 | 11 | 57.9 |
| Nephrotoxicity | 1 | 1 | 25.0 |
| | 2 | 3 | 75.0 |
| Dizziness | 2 | 1 | 100.0 |
| Hypokalemia | 1 | 3 | 10.7 |
| | 2 | 24 | 85.7 |
| | 3 | 1 | 3.6 |
| Hypomagnesaemia | 2 | 2 | 100.0 |
| Hyponatremia | 2 | 1 | 100.0 |
| IBS | 1 | 3 | 12.5 |
| | 2 | 21 | 87.5 |
| Hepatotoxicity | 2 | 10 | 100.0 |
| Gynecomastia | 1 | 2 | 50.0 |
| | 2 | 2 | 50.0 |
| Hypothyroidism | 1 | 5 | 45.5 |
| | 2 | 6 | 54.5 |
| Arthritis | 2 | 1 | 100.0 |
| GERD | 1 | 15 | 25.4 |
| | 2 | 43 | 72.9 |
| | 3 | 1 | 1.7 |
| PN | 1 | 11 | 19.3 |
| | 2 | 46 | 80.7 |
| Hypoalbuminemia | 1 | 3 | 50.0 |
| | 2 | 3 | 50.0 |
| Skin | 1 | 3 | 27.3 |
| | 2 | 8 | 72.7 |
| Depression | 1 | 3 | 75.0 |
| | 2 | 1 | 25.0 |

**Table 14** Side effect timings (month) among the studied cases.

| Side effects | Total | Median (IQR) | Range |
|---|---|---|---|
| Ototoxicity | 19 | 6.0 (5.0–7.0) | 2.0–10.0 |
| Nephrotoxicity | 4 | 1.0 (1.0–1.0) | 1.0–1.0 |
| Dizziness | 1 | | 3.0 |
| Hypokalemia | 28 | 3.0 (2.0–4.0) | 1.0–8.0 |
| Hypomagnesaemia | 2 | | 1.0–6.0 |
| Hyponatremia | 1 | | 2.0 |
| IBS | 24 | 4.0 (2.3–6.0) | 1.0–10.0 |
| Hepatotoxicity | 10 | 5.0 (2.8–6.3) | 1.0–8.0 |
| Gynecomastia | 4 | 6.0 (3.8–9.8) | 3.0–11.0 |
| Hypothyroidism | 11 | 6.0 (3.0–7.0) | 1.0–7.0 |
| Arthritis | 1 | | 7.0 |
| GERD | 59 | 3.0 (2.0–4.0) | 1.0–9.0 |
| PN | 57 | 3.0 (2.0–4.5) | 1.0–12.0 |
| Hypoalbuminemia | 6 | 3.0 (2.5–3.5) | 1.0–5.0 |
| Skin | 11 | 6.0 (4.0–7.0) | 3.0–12.0 |
| Depression | 4 | 5.0 (1.0–10.5) | 1.0–11.0 |

Second line drugs are frequently associated with very high rates of unacceptable adverse drug reactions, needing frequent interruption and change of regimen. Some authors reported that 41% of the patients experienced some side effects and only 21.1% of the patients required stoppage or change of drug in their study of 39 patients of MDR-TB [14].

Close monitoring of the patient is necessary to ensure that the adverse effects of second line drugs are recognized quickly. The ability to monitor patients for adverse effects daily is one of the major advantages of Directly Observed Treatment as in category IV treatment running as a pilot project in some states of India. The majority of adverse effects are easy to recognize. Commonly, patients will volunteer that they are experiencing adverse effects. However, it is important to have a systematic

**Table 15** Comparison between cases with and without ototoxicity as regards the prescribed anti-tuberculous drugs.

| Anti-tuberculous drugs | Present ($N = 19$) | Absent ($N = 88$) | #$P$ |
|---|---|---|---|
| Kanamycin | 13 (68.4%) | 40 (45.5%) | 0.069 |
| Amikacin | 4 (21.1%) | 29 (33.0%) | 0.308 |
| Ethambutol | 0 (0.0%) | 22 (25.0%) | 0.014* |
| Capreomycin | 1 (5.3%) | 13 (14.8%) | 0.265 |
| Streptomycin | 1 (5.3%) | 6 (6.8%) | 0.804 |

# Chi square test.
* Significant.

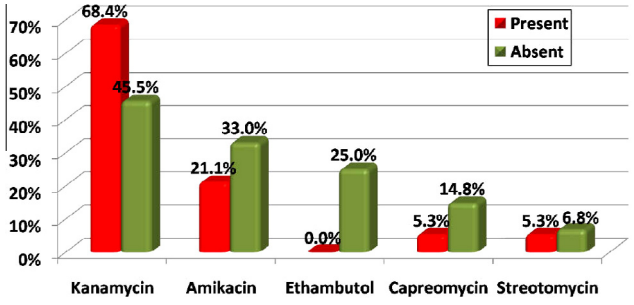


**Figure 6** Comparison between cases with and without ototoxicity as regards the prescribed anti-tuberculous drugs.

**Table 16** Comparison between cases with and without hypokalemia as regards the prescribed anti-tuberculous drugs.

| Anti-tuberculous drugs | Present ($N = 28$) | Absent ($N = 79$) | #$P$ |
|---|---|---|---|
| Kanamycin | 12 (42.9%) | 41 (51.9%) | 0.411 |
| Amikacin | 9 (32.1%) | 24 (30.4%) | 0.862 |
| Ethambutol | 4 (14.3%) | 18 (22.8%) | 0.339 |
| Capreomycin | 2 (7.1%) | 12 (15.2%) | 0.278 |
| Streptomycin | 2 (7.1%) | 5 (6.3%) | 0.881 |

# Chi square test.

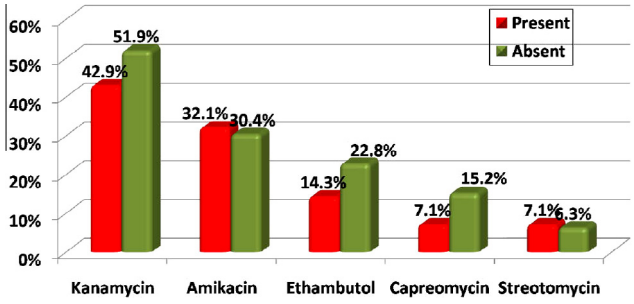


**Figure 7** Comparison between cases with and without hypokalemia as regards the prescribed anti-tuberculous drugs.

**Table 17** Comparison between cases with and without IBS as regards the prescribed anti-tuberculous drugs.

| Anti-tuberculous drugs | Present ($N = 24$) | Absent ($N = 83$) | #P |
|---|---|---|---|
| Kanamycin | 12 (50.0%) | 41 (49.4%) | 0.959 |
| Amikacin | 5 (20.8%) | 28 (33.7%) | 0.228 |
| Ethambutol | 3 (12.5%) | 19 (22.9%) | 0.267 |
| Capreomycin | 1 (4.2%) | 13 (15.7%) | 0.141 |
| Streptomycin | 3 (12.5%) | 4 (4.8%) | 0.180 |

# Chi square test.

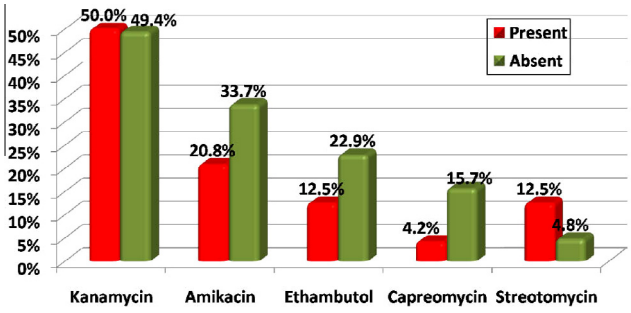


**Figure 8** Comparison between cases with and without IBS as regards the prescribed anti-tuberculous drugs.

**Table 18** Comparison between cases with and without hepatotoxicity as regards the prescribed antituberculous drugs.

| Anti-tuberculous drugs | Present ($N = 10$) | Absent ($N = 97$) | #P |
|---|---|---|---|
| Kanamycin | 2 (20.0%) | 51 (52.6%) | 0.054 |
| Amikacin | 5 (50.0%) | 28 (28.9%) | 0.168 |
| Ethambutol | 1 (10.0%) | 21 (21.6%) | 0.385 |
| Capreomycin | 1 (10.0%) | 13 (13.4%) | 0.761 |
| Streptomycin | 1 (10.0%) | 6 (6.2%) | 0.642 |

# Chi square test.

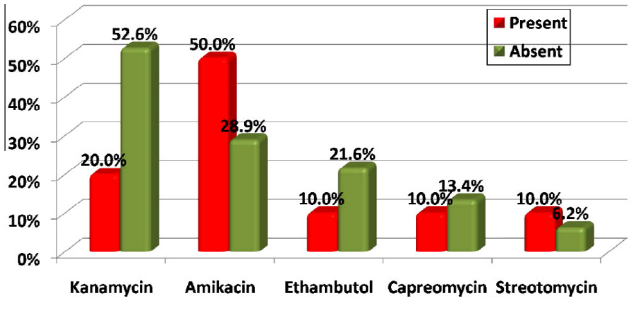


**Figure 9** Comparison between cases with and without hepatotoxicity as regards the prescribed antituberculous drugs.

method of patient interviewing since some patients may be reticent about reporting even severe adverse effects. Other patients may be distracted by one adverse effect and forget to tell the physician about others. The physician should be

**Table 19** Comparison between cases with and without hypothyroidism as regards the prescribed antituberculous drugs.

| Anti-tuberculous drugs | Present ($N = 11$) | Absent ($N = 96$) | #P |
|---|---|---|---|
| Kanamycin | 9 (81.8%) | 44 (45.8%) | 0.024* |
| Amikacin | 1 (9.1%) | 32 (33.3%) | 0.099 |
| Ethambutol | 1 (9.1%) | 21 (21.9%) | 0.320 |
| Capreomycin | 0 (0.0%) | 14 (14.6%) | 0.174 |
| Streptomycin | 0 (0.0%) | 2 (2.1%) | 0.629 |

# Chi square test.
* Significant.

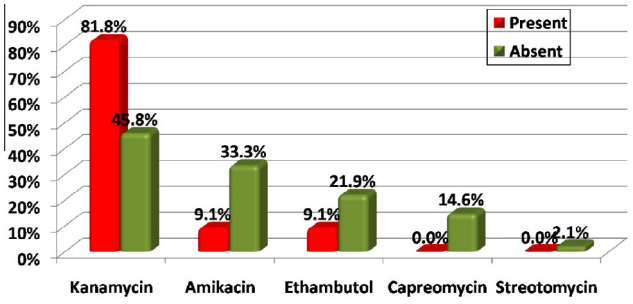


**Figure 10** Comparison between cases with and without hypothyroidism as regards the prescribed antituberculous drugs.

**Table 20** Comparison between cases with and without GIT manifestations as regards the prescribed anti-tuberculous drugs.

| Anti-tuberculous drugs | Present ($N = 61$) | Absent ($N = 46$) | #P |
|---|---|---|---|
| Kanamycin | 20 (32.8%) | 13 (28.3%) | 0.616 |
| Amikacin | 22 (36.1%) | 17 (37.0%) | 0.924 |
| Ethambutol | 7 (11.5%) | 6 (13.0%) | 0.922 |
| Capreomycin | 7 (11.5%) | 6 (13.0%) | 0.922 |
| Streptomycin | 5 (8.2%) | 4 (8.7%) | 0.927 |

# Chi square test.

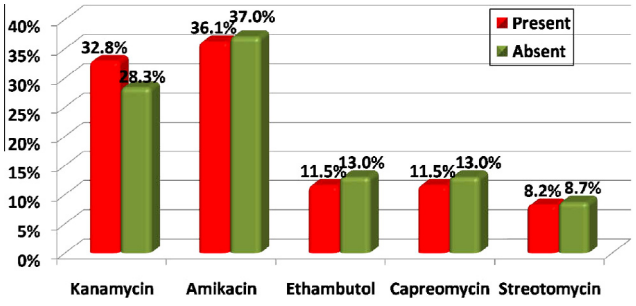


**Figure 11** Comparison between cases with and without GIT manifestations as regards the prescribed anti-tuberculous drugs.

trained to screen patients regularly for symptoms of common adverse effects: rashes, gastrointestinal symptoms (nausea, vomiting, diarrhea), psychiatric symptoms (psychosis, anxiety,

**Table 21** Comparison between cases with and without PN as regards the prescribed anti-tuberculous drugs.

| Anti-tuberculous drugs | Present ($N = 57$) | Absent ($N = 50$) | #$P$ |
|---|---|---|---|
| Kanamycin | 32 (56.1%) | 21 (42.0%) | 0.144 |
| Amikacin | 13 (22.8%) | 20 (40.0%) | 0.055 |
| Ethambutol | 9 (15.8%) | 13 (26.0%) | 0.192 |
| Capreomycin | 1 (12.3%) | 13 (14.0%) | 0.792 |
| Streptomycin | 2 (3.5%) | 5 (10.0%) | 0.175 |

# Chi square test.

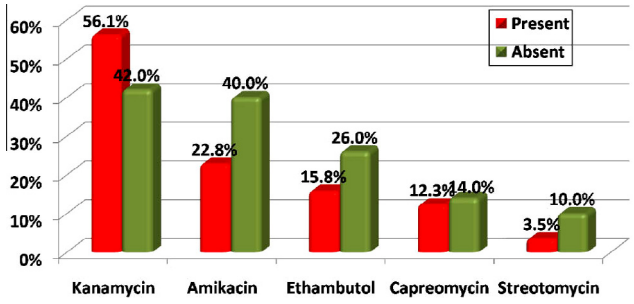


**Figure 12** Comparison between cases with and without PN as regards the prescribed anti-tuberculous drugs.

depression, suicidal ideation), jaundice, ototoxicity and peripheral neuropathy [15].

Prompt evaluation, diagnosis and treatment of adverse effects are extremely important, even if the adverse effect is not particularly dangerous. If the adverse effect is mild and not dangerous like peripheral neuropathy in our patient, continuing the treatment regimen, with the help of ancillary drugs if needed, is often the best option [16].

The patient receives the following regimen, if proved to be MDR-TB:

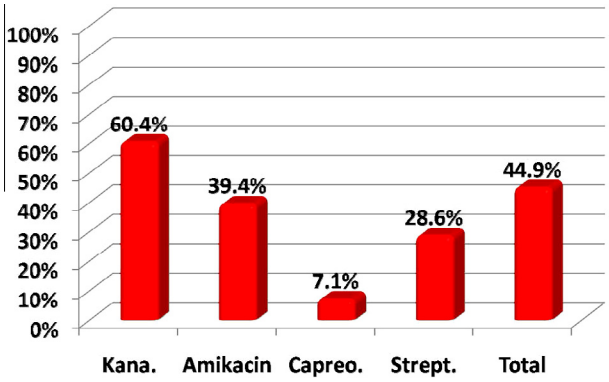


**Figure 13** Comparison between Anti-TB regimens regarding PN.

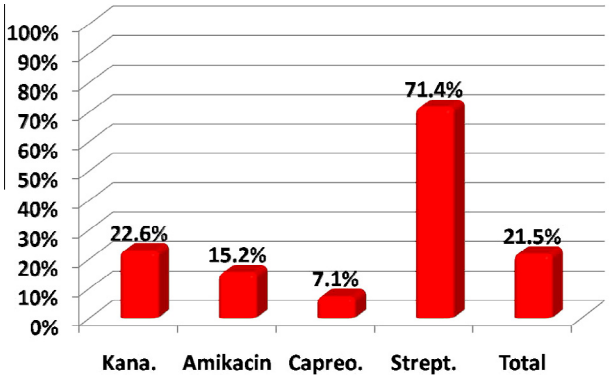


**Figure 14** Comparison between Anti-TB regimens regarding IBS.

- Kanamycin daily for three months then every other day,
- + Levofloxacin,
- + Ethionamide,
- + Cycloserine or + PAS.

**Table 22** Comparison between Anti-TB regimens regarding complications.

| Complication | Kanamycin ($N = 53$) | Amikacin ($N = 33$) | Capreomycin ($N = 14$) | Streptomycin ($N = 7$) | Total ($N = 107$) | ^$P$ |
|---|---|---|---|---|---|---|
| Ototoxicity | 13 (24.5%) | 4 (12.1%) | 1 (7.1%) | 1 (14.3%) | 19 (17.8%) | 0.380 |
| Renal impairment | 3 (5.7%) | 1 (3.0%) | 0 (0.0%) | 0 (0.0%) | 4 (3.7%) | 1.000 |
| Dizziness | 0 (0.0%) | 1 (3.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.9%) | 1.000 |
| Hypomagnesaemia | 0 (0.0%) | 1 (3.0%) | 1 (7.1%) | 0 (0.0%) | 2 (1.9%) | 0.225 |
| Hyponatremia | 0 (0.0%) | 0 (0.0%) | 1 (7.1%) | 0 (0.0%) | 1 (0.9%) | 0.196 |
| Gynecomastia | 1 (1.9%) | 1 (3.0%) | 0 (0.0%) | 1 (14.3%) | 3 (2.8%) | 0.291 |
| Arthritis | 1 (1.9%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.9%) | 1.000 |
| Hypoalbuminemia | 4 (7.5%) | 2 (6.1%) | 0 (0.0%) | 0 (0.0%) | 6 (5.6%) | 0.904 |
| Skin disorders | 5 (9.4%) | 5 (15.2%) | 0 (0.0%) | 1 (14.3%) | 11 (10.3%) | 0.434 |
| Depression | 3 (5.7%) | 1 (3.0%) | 0 (0.0%) | 0 (0.0%) | 4 (3.7%) | 1.000 |
| GERD | 35 (66.0%) | 15 (45.5%) | 5 (35.7%) | 4 (57.1%) | 59 (55.1%) | 0.108 |
| PN | 32 (60.4%) | 13 (39.4%) | 1 (7.1%) | 2 (28.6%) | 48 (44.9%) | $< 0.001$* |
| Hypokalemia | 12 (22.6%) | 9 (27.3%) | 2 (14.3%) | 2 (28.6%) | 25 (23.4%) | 0.782 |
| IBS | 12 (22.6%) | 5 (15.2%) | 1 (7.1%) | 5 (71.4%) | 23 (21.5%) | 0.011* |
| Hepatotoxicity | 2 (3.8%) | 5 (15.2%) | 1 (7.1%) | 1 (14.3%) | 9 (8.4%) | 0.193 |
| Hypothyroidism | 9 (17.0%) | 1 (3.0%) | 0 (0.0%) | 0 (0.0%) | 10 (9.3%) | 0.104 |

^ Fisher Exact test.
* Significant.

**Table 23** Comparison between DM and non-DM cases as regards the different side effects among the studied cases.

| Side effects | DM ($N$ = 32) | Non-DM ($N$ = 75) | #$P$ |
|---|---|---|---|
| Ototoxicity | 9 (28.1%) | 10 (13.3%) | 0.067 |
| Nephrotoxicity | 3 (9.4%) | 1 (1.3%) | 0.045* |
| Dizziness | 0 (0.0%) | 1 (1.3%) | 0.512 |
| Hypokalemia | 9 (28.1%) | 19 (25.3%) | 0.764 |
| Hypomagnesaemia | 1 (3.1%) | 1 (1.3%) | 0.531 |
| Hyponatremia | 0 (0.0%) | 1 (1.3%) | 0.512 |
| IBS | 6 (18.8%) | 18 (24.0%) | 0.551 |
| Hepatotoxicity | 6 (18.8%) | 4 (5.3%) | 0.029* |
| Gynecomastia | 1 (3.1%) | 2 (2.7%) | 0.895 |
| Hypothyroidism | 1 (3.1%) | 10 (13.3%) | 0.111 |
| Arthritis | 1 (3.1%) | 0 (0.0%) | 0.124 |
| GERD | 16 (50.0%) | 43 (57.3%) | 0.485 |
| PN | 14 (43.8%) | 43 (57.3%) | 0.197 |
| Hypoalbuminemia | 4 (12.5%) | 2 (2.7%) | 0.043* |
| Skin | 2 (6.3%) | 9 (12.0%) | 0.370 |
| Depression | 1 (3.1%) | 3 (4.0%) | 0.827 |

# Chi square test.
* Significant.

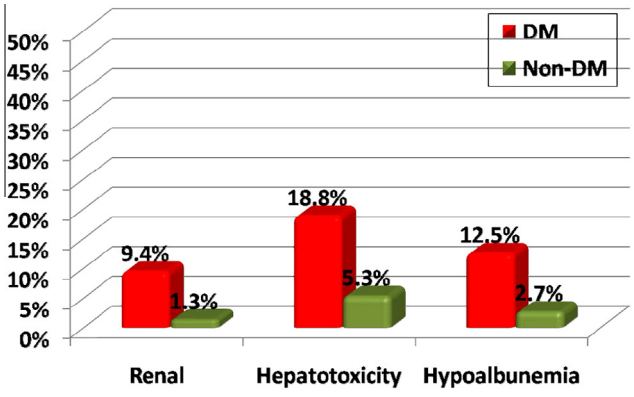


**Figure 15** Comparison between DM and non-DM cases as regards the different side effects among the studied cases.

- Pyrazinamide is recommended to be added to every regimen at least during the intensive phase.

It must be noticed that the total duration of injection is at least 8 months, as a total duration, or at least 6 months after sputum conversion and, the total duration of treatment course is at least 20 months. The duration could be extended to other three months. The same is applicable for the total duration of treatment [4].

Timely and aggressive management of adverse effects is essential. Without it, mortality and permanent morbidity can be the result, in addition to patient non-adherence. Even if the adverse effects are not particularly dangerous, prompt intervention is important. Patients may have significant anxiety about an adverse effect if they do not understand why it is happening. This may in turn augment the severity of the adverse effect, eg. nausea and vomiting [17].

The current study is a retrospective one to assess side effects of second-line TB drugs in patients treated for MDR-TB at Abbassia Chest Hospital from 1st of January 2009 till 1st of January 2012.

This study included 107 patients admitted at MDR ward at Abbassia Chest Hospital, patients who were readmitted to the ward were excluded.

All the patients received second line antituberculous drugs:

- Kanamycin (54)
- Amikacin (34)
- Ethionamide (107)
- Capreomycin (14)
- Cycloserine (107)
- PAS (107)
- Ofloxacin (107)
- Streptomycin (2)

In this study, the mean of age was 37.1 years, representing the period of physical, mental and occupational stress. This result did not coincide with that of Madkour et al. [18], who stated that in Sayeda Zeinab district, TB was mainly a disease of adults between 20 and 29 years of age. This difference might be due to that Madkour et al's. study was done in a localized area (Sayeda Zeinab) that gave small representative data and also their study was not a recent one and so not all cases of TB had been discovered and had been registered. On the other hand the result matched with those of Sagwa et al. [19], who reported that the mean age group was 34.7 years and those of Törün et al. [20], who stated that the mean age group was 37.8 years. Also, this result coincided with Isaakidis et al. [21], who showed that the mean age group was 35.5 years, and supported by Modongo and Zetola [22], who stated that the mean age was 37 years.

In this study, males were 78 cases (72.9%) and females were 29 cases (27.1%). This coincides with the epidemiological picture of tuberculosis where males are more exposed to infection in the community than females because of occupational and mental stress or other social factors which prevent females from seeking medical advice, which may cause a false lowering of the incidence rate in females. This result coincided with Chung-Delgado et al. [23], who reported that the percentage of MDR-TB males was 76% and that of females was 24%. This result is also in agreement with Törün et al. [20], who reported that 79% of MDR-TB patients in their study were males and 21% were females. Also, it matched with Sagwa et al. [19], who reported that 66% of MDR-TB patients in their study were males and 34% were females.

It was noticed that the most frequent special habit among the studied cases was tobacco smoking [29 cases (27.1%)], followed by drug addiction [6 cases (5.6%)] and the third was alcohol intake [4 cases (3.7%)]. This result did not coincide with that of Fawzy et al. [24], who reported that there was no statistical relation as regards smoking among TB patients. Fawzy et al. study included only 21 MDR patients admitted at Abbassia Chest Hospital as well as in Chest Clinics in Cairo. This difference might be due to that the data of the patients in chest clinics might not be so accurate specially as regarding special habits of the patients. Also, this result did not coincide with that of Kamal et al. [25], who revealed that in MDR TB, smokers were 61.53% and non smokers were 38.47%. There was no significant difference detected between smokers and non smokers MDR TB patients. This difference may be explained by a relatively small number of patients upon which this study was done {only 26 MDR TB patients} and it covered a short period of time (from January 2005 to

December 2005). Oppositely, this result coincided with Safwat et al. [26], who reported that 35% of the patients were smokers and 11.1% were addict.

In this study, the most common co-morbidity associated with MDR TB was diabetes {32 cases (29.9%)}, followed by chronic chest diseases as chronic obstructive lung disease {12 cases (11.2%)}. This result agreed with those of Törün et al. [20], who reported that the highest co-morbidity among MDR-TB patients was DM 17.8% of the patients then COPD (2.2%). Also, it matched with those of Safwat et al. [26], who reported that the highest co-morbidity among MDR-TB patients was DM (18.3%) of the patients then COPD (8.9%). On the other hand, this result did not coincide with those of Fouad et al. [27], who reported that there was no correlation between diabetes mellitus and drug resistance. This difference might be due to controllability of the disease, state of immunity and age of the patients.

In this study, acquired resistance was 95.3% and primary resistance was 4.7%. This might be due to lack of patients' adherence to chemotherapy or inappropriate regimen of treatment. This result was supported with those of Abd El Hamid et al. [28], who found that the acquired MDR-TB cases exceeded the primary MDR-TB cases. The acquired resistance was 72%, while the primary resistance was 38%. Also; this result coincided with those of Tag El Din et al. [29], who found that the acquired MDR-TB cases exceeded the primary MDR-TB cases. The acquired resistance was 72% while the primary resistance was 28%.

In the present study, cured patients were 99 cases (92.5%), dead patients were 7 cases (6.5%) and defaulters were 1 case (0.9%). This result did not match with those of Mota et al. [30], who reported that 67% died, 13% had a favorable outcome, and 9% were defaulters. Also, the result did not match with those of Isaakidis et al. [21], who reported that 19.4% were successfully treated, 20.9% died, defaulted 13.4%. This difference might be due to that Isaakidis et al., study enrolled 67 patients only. On the other hand, the result coincided with Shin et al. [31], who studied the outcome of treatment of MDR TB patients with standardized regimens and reported that 76.0% were cured, 4.9% died and 11.5% defaulted. Again, the result matched with those of Anderson et al. [32], who reported that 70.6% were cured, 6.9% died.

The 94.4% prevalence of adverse events observed in the current study is higher than that reported in other studies, Bloss et al. [33] and Nathanson et al. [15], where it ranged from 69% to 86%. It was slightly lower than the 96% reported by Tupasi et al. [34] in their study of 117 patients in the Philippines. The reasons for the heterogeneity in the prevalence of adverse events across the various studies are unclear, but might be related to several possible factors such as: differences in definitions of adverse event terminologies across settings, whether the adverse event was symptomatic and patient-reported (subjective) or clinician-validated (objective), whether all or only the severe and serious adverse events were studied, variations in the use of specific anti-TB agents, and/or the differences in co-morbidities and other covariates between study settings.

In the present study, the frequency of side effects of prescribed drugs was as follows; GERD 57%, peripheral neuritis 53.3%, hypokalemia 26.2%, irritable bowel syndrome 22.4%, ototoxicity 17.8%, skin reaction 10.3%, hypothyroidism 10.3%, hepatotoxicity 9.3%, hypoalbuminemia 5.6%, depression 3.7%, arthritis 0.9%, gynecomastia 2.8%, hyponatremia 5.6%, hypomagnesaemia 1.9%, dizziness 0.9% and nephrotoxicity 3.7%. This result coincides with those of El-Naggar et al. [35], who stated that the most frequent side effects of Anti TB drugs were gastrointestinal manifestations (84%) and peripheral neuritis (58.4%). Also, this result agreed with those of Safwat et al. [26], who reported that adverse effects were as follows: 88.8% Gastrointestinal, peripheral neuritis 76.7% and hypokalemia 23.3%. Oppositely, the result did not coincide with those of Törün et al. [20], who reported that the highest adverse effects were ototoxicity 41.8%, Psychological 21.3% and Gastrointestinal 14%. This difference might be due to the fact that Törün study included 263 MDR TB patients who received individualized treatment for MDR-TB between April 1992 and June 2004 at Istanbul, Turkey and also the author said that the frequent and early occurrence of ototoxicity may be due to the extended exposure to amino glycosides and Capreomycin during or prior to MDR-TB treatment. Again, the result did not match with that of Jacobs and Ross [36], who reported that the highest adverse effects were ototoxicity (28.7%); peripheral neuropathy (23.2%); diarrhea, nausea and vomiting (20.5%). This difference might be due to the fact that Jacobs' study enrolled 350 MDR TB patients from South African Chest Clinic, the majority of chest clinic's patients were retreatment cases.

Among 107 patients who were screened for electrolyte abnormalities, 26.2% had hypokalemia, defined as a potassium level of $<3.5$ mEq/L. Diagnosis of low serum potassium occurred, on average, after 3 months of individualized therapy. Multivariate analysis of risk factors for this adverse reaction identified two causes: administration of Capreomycin, and low initial body weight. Comparison between cases with and without hypokalemia as regards prescribed anti-tuberculous showed that there was no significant difference between them and this may be because the patients received other drugs rather than aminoglycosides that can cause hypokalemia. This result partially coincides with that of Shin et al. [37], who reported that 31% of the cases developed hypokalemia and said that it might be due two causes: administration of Capreomycin, and low initial body weight.

In our study, nephrotoxicity frequency was 3.7%, due to amino glycosides, but was not as high as ototoxicity (17.8%), and this was similar to the results of Furin et al. [38], Jager and Altena [39]. Three cases were major (need stoppage or withdrawal of the drug) and one case was minor (no stoppage or withdrawal of the drug but just follow up) and that coincided with Törün et al. [20], who reported 2 cases with nephrotoxicity and they were major.

In the current study, 19 cases developed ototoxicity (17.8%), 2 of them were minor, and 17 were major, and that was similar to the results of Törün et al. [20], who reported that the majority of cases who developed ototoxicity needed stoppage or withdrawal of the drug (major side effects).

In our study, hepatotoxicity was not rare {(10 cases) 9.3%}. Once this side effect had occurred, all drugs were suspended until liver function tests return to baseline. Gradually introducing the drugs by giving them in increasing number and dosage is recommended. Those drugs most commonly associated with hepatotoxicity should be added last. All the cases had hepatotoxicity as a major side effect and that did not coincide with the results of Törün et al. [20], who reported 8 cases as a major and 4 cases as a minor. This difference might be

attributed to the difference in the number of enrolled cases in each study, drugs prescribed or the duration of treatment and follow up.

Psychiatric disorders were also observed in 4 patients (3.7%) under treatment who suffered from depression and this was partly attributable to a loss of confidence in the health services due to previous treatment failures. Patients' trust in the treatment they are receiving is crucial if they are to continue with such a long treatment regimen. Treatment managers need to be aware of this and ensure that staff administering treatment regimens do all they can to win the trust and build the confidence of the patients in their care. Some drugs used in MDR-TB treatment also cause psychiatric disorders. Psychosis has been reported as a side effect of CS and fluoroquinolones, and depression, while it has been associated with other drugs in the MDR-TB treatment regimen, is primarily associated with CS [40]. In response to psychosis and depression, we initiated antidepressant or anti-psychotic therapy as and when needed.

In the current study and according to the severity code, GIT side effects were 26.2% mild and 73.7% moderate and that did not coincide with the results of Isaakidis et al. [21], who reported that 24% of GIT symptoms were mild and 12% were moderate. This difference might be due to the fact that Isaakidis et al. enrolled 67 patients only in their study.

In our study and according to the severity code, 19.3% of the peripheral neuritis cases were mild and 80.7% were moderate and this partially matched with the results of Isaakidis et al. [21], who reported that 4% of PN symptoms were mild and 21% were moderate.

Hypothyroidism developed in only 10.3% of studied patients and that coincided with Furin et al. [38], who reported a 10% level of hypothyroidism in their series.

Most adverse reactions occurred during the first 3 months of treatment. Every effort was made to avoid permanent discontinuation of any anti-tuberculosis drug unless the adverse reaction was life threatening or could not be controlled otherwise. These results match partially with those of Törün et al. [20], who reported that the adverse effects began 4 months after beginning of treatment. In addition, this result was supported with those of Isaakidis et al. [21], who reported that the adverse effects occurred between 2nd, and 4th month of MDR-TB treatment initiation and those of Van der Walt et al. [41], who reported that the adverse effects occurred during the first 4 months of MDR-TB treatment. On the other hand, this result did not agree with those of Shin et al. [31], who reported that most adverse reactions occurred during the first 8 months of treatment. This difference might be due to the fact that in Shin study, there were 244 MDR TB patients enrolled from Russia and the duration of the study was only two years between 10 September 2000 and 10 September 2002.

In our study, comparison between cases with and without ototoxicity as regards the prescribed anti-tuberculous drugs showed that there was no significant relation between Kanamycin and ototoxicity and this result coincided with that of Duggal and Sarkar [42].

In our study, comparison between cases with and without peripheral neuritis as regards the prescribed anti-tuberculous drugs showed that there was no significant relation between it and any prescribed antibiotic. This result agreed with that of Shin et al. [16], who reported that although there was a tendency for patients with peripheral neuropathy to be older, male and have co-morbid conditions, these variables were not statistically significant.

In our study, side effects occurred more in non diabetics (70%) compared to diabetic patients (29.9%) and this might be due to the fact that the number of diabetic patients included was low (32). This result coincided with that of Chung-Delgado et al. [23], who reported that 92.7% of patients were non diabetics and 7.4% were diabetic.

## Limitation of the study

By using retrospective data, we encountered instances of missing patient treatment records and missing data on specific variables. Furthermore, it was not possible to perform qualitative causality assessment of the adverse events using the available data, especially given the paucity of laboratory data. The adverse events recorded on the patients' side effect monitoring form were based on patient-reported symptoms. Hence, there was a possibility of subjectivity and of selective under-reporting of adverse events by patients or the selective recording of adverse events by clinicians, which may have biased the results away from the true prevalence. Some symptoms of reported adverse events may have overlapped with symptoms of the co-morbidities.

## Conclusions

- There is a relation between both tobacco smoking and drug addiction, and MDR TB.
- The most common type of resistance is acquired resistance because of lack of adherence to treatment or inappropriate treatment.
- No statistical difference between males and females according to associated diseases or drug sensitivity test.
- The most common co-morbidities associated with MDR TB are diabetes and chronic obstructive lung diseases.
- The most important predictors of patients' outcome are sputum conversion, number of previous TB treatment and presence of co-morbidities.

## Recommendations

- Regular drug resistance survey is important to monitor the cases.
- The best way to prevent MDR is: early detection and prompt treatment of TB.
- In the light of increasing incidence of resistance of tuberculosis, it is recommended that drug susceptibility testing should be done for all patients if feasible.
- The application of the Directly Observed Therapy with short course chemotherapy should be very strict to eliminate the problem of non adherence to therapy.
- To limit the resistance to Streptomycin and Rifampicin, they should not be prescribed for diseases other than tuberculosis.
- Restricted availability of Rifampicin and Streptomycin in private pharmacies except by prescription.
- There is an urgent need to develop new anti-tuberculous drugs to shorten the duration of treatment and to make development of resistance less likely to emerge.

- Health education about TB and hazards of tobacco smoking and drug addiction.
- In TB patients with associated diseases, these associated diseases should be well controlled, especially diabetes.
- Adherence of patients to treatment even at home is more important than admission at hospital because resistance is more liable to occur at hospital.
- Regular follow up of treatment to detect early side effects of medications.

## Conflict of interest

There is no conflict of interest.

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