Management of Adverse reactions events in the treatment of MDR-TB

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WHO International Training Centre on Treatment and Management of MDR-TB
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Presentation outline

• Monitoring of adverse reactions
• Strategies for management of adverse reactions
• Frequency of adverse reactions associated with second line drugs
Definitions

• **Allergic reaction**: IgE - mast cell - histamine axis; may be mild (itching, rash) or fatal (anaphylaxis)

• **Toxic effect**: tissue or organ injury or damage (functional or structure), that may lead to irreversible harm or death if not managed properly

• **Side effect**: reversible, unpleasant but not intrinsically dangerous reaction to drug (unless prolonged, untreated)
Monitoring of adverse drug reactions

• Monitoring of drug side effects should be provided full course of treatment
• Daily observation by DOT provider,
• Monitoring for adverse effects monthly
• Patients should be informed about side effects
• All side effects should be registered
Monitoring Schedule

• Daily check during DOT –
  – Symptoms of allergy,
  – side effects,
  – adverse drug reactions (ADRs)

• Monthly clinical evaluation by MD: examination for symptoms and signs of ADRs
  – skin rash due to drug allergy
  – bedside tests of hearing (audiometry) and vision (color, visual fields, acuity)
  – dehydration, malnutrition due to anorexia, vomiting, diarrhea
  – abdominal tenderness, jaundice due to hepatotoxicity
Monitoring Schedule

• Monthly clinical evaluation by MD, continued:
  – dry skin, slow reflexes, eyelid lag due to thyrotoxicity of ETA/PTA, PAS
  – muscle cramps, palpitations, fluid retention due to nephrotoxicity of aminoglycosides
  – Mental status examination, sleep disturbances due to CNS effects of cycloserine, quinolones
  – tenderness in joints, connective tissue due to quinolones
Monitoring Schedule

• Monthly lab tests during intensive phase
  – Creatinine, electrolytes (Serum potassium)
  – at baseline, then at least monthly while receiving an injectable drug
  – liver enzymes,
  – optometry, audiometry, electrocardiography

• Quarterly throughout
  – liver enzymes, (electrocardiogram), (depression inventory)

• Otherwise, depending on patient-specific side effects and drug toxicity
  – Thyroid stimulating hormone TSH (FT₃, FT₄), - At baseline and at, ideally once between months 6-9 if receiving ethionamide and/or PAS; and monitor for signs/symptoms of hypothyroidism
  – uric acid
Management of adverse reactions - standard protocols for registration - 4

Registration of adverse reactions form

Patient name................ Name of the institution..............................
Physician................................
Repeat measurements monthly (after intensive phase every three months)

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Date</th>
<th>Regimen</th>
<th>Adverse reaction related drug</th>
<th>Treatment of adverse reaction</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
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</table>
Strategies for management of adverse reactions
Side effects may be different by the severity

- **Mild** - treatment regimen not changed
- **Moderate** – interruption of causative drug or all drugs for short time
- **Severe** – discontinuation of causative drug
Life threatening adverse events

- Anaphylaxis
- Severe toxic allergic reactions (exfoliative dermatitis, Steeven-Johnson syndrome)
- Severe gastritis with bleeding
- Severe hepatitis
- Renal failure
- Severe electrolytes disturbances
Specific trainings on adverse events to second-line drugs

– Ensured training and education based on task analysis for HCW
– Ongoing patient education is provided
– Compliance with MDR-TB treatment of staff and patients achieved
– Good communication and psychosocial support for patients
Management of adverse reactions

- Altering dosages when appropriate
- In case of need discontinuation of some drugs
- Avoid of additional drug resistance development during management of side effects
Use of ancillary drugs to treat adverse events

<table>
<thead>
<tr>
<th>Indication</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea, vomiting, stomach upset</td>
<td>Metoclopramide, dimenhydrinate prochlorperazine, promethazine, bismuth subsalicylate, H2-blockers and proton pump inhibitors etc.</td>
</tr>
<tr>
<td>Heartburn, sour stomach, ulcer</td>
<td></td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td>Fluconazole, clotrimazole</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Loperamide</td>
</tr>
<tr>
<td>Cutaneous reactions, itching</td>
<td>Hydrocortisone cream, calamine, aladryl lotions, Antihistamines, steroids (prednisone, dexamethasone)</td>
</tr>
<tr>
<td>Systemic hypersensitivity reactions</td>
<td>oral steroids (prednisone), injectable steroids (dexamethasone, methylprednisolone)</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>Inhaled beta-agonists (albuterol, etc.), inhaled corticosteroids, (beclomethasone, etc.),</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Levo-thyroxine</td>
</tr>
<tr>
<td>Electrolyte wasting</td>
<td>Potassium and magnesium replacement</td>
</tr>
</tbody>
</table>
## Use of ancillary drugs to treat adverse events - continue

<table>
<thead>
<tr>
<th>Condition</th>
<th>Drugs/Compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis of neurological complications of cycloserine</td>
<td>Vitamine B6</td>
</tr>
<tr>
<td>Depression</td>
<td>Selective serotonin reuptake inhibitors (fluoxetine, sertraline), tricyclic antidepressants (amitriptyline)</td>
</tr>
<tr>
<td>Severe anxiety</td>
<td>Lorazepam, diazepam, clonazepam</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Dimenhydrinate</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Haloperidol, thorazine, risperidone</td>
</tr>
<tr>
<td>Seizures</td>
<td>Phenytoin, carbamazepine, valproic acid, phenobarbital</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Pyridoxine (vitamin B6) Amitriptyline, Meclizine, dimenhydrinate, prochlorperazine, promethazine</td>
</tr>
<tr>
<td>Vestibular symptoms</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain, arthralgia, headache</td>
<td>Ibuprofen, paracetamol, codeine</td>
</tr>
</tbody>
</table>
Frequency of adverse reactions associated with second line drugs
**Adverse events - results from 5 DOTS-Plus projects**

- Only 2% of patients stopped treatment but 30% required removal of the suspected drug(s) from the regimen due to adverse events.

- The five most common adverse events were:
  - nausea/vomiting (32.8%)
  - diarrhoea (21.1%)
  - arthralgia (16.4%)
  - dizziness/vertigo (14.3%)
  - hearing disturbances (12.0%)
Frequency of Specific Side Effects Cohort 2000, Latvia

Percent of patients with specific side effect

- **Nausea**: 73%
- **Vomiting**: 38.7%
- **Abdominal pain**: 38.2%
- **Dizziness**: 35.8%
- **Hearing loss**: 28.4%
- **Diarrhea**: 27%
- **Joint pain**: 18.6%
- **Itching**: 16.7%
- **Neuropathy**: 15.7%
- **Headache**: 14.7%
- **Psychiatric**: 14.2%
- **Vestibular reaction**: 12.3%
- **Skin rash**: 12.3%
- **Hematologic effects**: 11.3%
- **Hepatitis**: 11.3%

Side effects
Adverse events 5 DOTS-Plus projects
Treatment continuity in patients enrolled on MDR-TB treatment

- Patients that stopped treatment due to adverse reactions
- Patients that required drug removal from the regimen due to adverse reactions

<table>
<thead>
<tr>
<th>Country</th>
<th>Patients that stopped treatment</th>
<th>Patients that required drug removal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estonia</td>
<td>3</td>
<td>43</td>
</tr>
<tr>
<td>Latvia</td>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td>Peru</td>
<td>0</td>
<td>34</td>
</tr>
<tr>
<td>Philippines</td>
<td>8</td>
<td>49</td>
</tr>
<tr>
<td>Tomsk</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>30</td>
</tr>
</tbody>
</table>

Percent

- Patients that stopped treatment due to adverse reactions
- Patients that required drug removal from the regimen due to adverse reactions
Management of adverse effects on MDR-TB treatment regimen for 367 patients

- 48 – Treatment alteration
- 61% - no adverse effects
- 24% - MDR-TB treatment stopped
- 13.4% - discontinued causing agent
- 1.6% - severe co-morbidities
- 2 - extensive drug resistance
- 1 - refused to restart treatment after Steeven-Johnson syndrome

89 - discontinued causing agent
## Patients with Drug Permanently Stopped

**Year 2000, N = 204 patients**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Month 1-6</th>
<th>Month 7-12</th>
<th>Month 13-18</th>
<th>Total # Over Course of Therapy</th>
<th>Total Patients Using Drug</th>
<th>Total % of All Persons on Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAS</td>
<td>21</td>
<td>12</td>
<td>1</td>
<td>35</td>
<td>125</td>
<td>28%</td>
</tr>
<tr>
<td>Prothionamide</td>
<td>20</td>
<td>12</td>
<td>6</td>
<td>36</td>
<td>187</td>
<td>19%</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>18</td>
<td>7</td>
<td>2</td>
<td>26</td>
<td>136</td>
<td>19%</td>
</tr>
<tr>
<td>Thiacetazone</td>
<td>13</td>
<td>6</td>
<td>6</td>
<td>25</td>
<td>180</td>
<td>14%</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>11</td>
<td>123</td>
<td>9%</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>8</td>
<td>5</td>
<td>1</td>
<td>13</td>
<td>149</td>
<td>9%</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>6</td>
<td>5</td>
<td>1</td>
<td>12</td>
<td>171</td>
<td>7%</td>
</tr>
</tbody>
</table>
Number of drugs causing adverse effects for one patient (total 145 patients)

- One drug: 87 (60.5%)
- Two drugs: 34 (23%)
- Three drugs: 11 (7.5%)
- Four drugs: 8 (6%)
- Five drugs: 5 (3%)
### Mean interval from initiation of Tx to occurrence of adverse effects

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Patients n ( % )</th>
<th>Mean interval from initiation of Tx to occurrence of adverse event (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild gastritis</td>
<td>60 ( 100 )</td>
<td>Not available</td>
</tr>
<tr>
<td>Dermatological effects</td>
<td>26 ( 43,3 )</td>
<td>Not available</td>
</tr>
<tr>
<td>Peripheral NS</td>
<td>12 ( 20 )</td>
<td>9,0</td>
</tr>
<tr>
<td>Depression</td>
<td>11 ( 18,3 )</td>
<td>9,1</td>
</tr>
<tr>
<td>Anxiety</td>
<td>7 ( 11,7 )</td>
<td>8,5</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>6 ( 10 )</td>
<td>10,8</td>
</tr>
<tr>
<td>Psychotic symptoms</td>
<td>6 ( 10 )</td>
<td>3</td>
</tr>
</tbody>
</table>
## Mean interval from initiation of Tx to occurrence of adverse effect

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>Patients n ( % )</th>
<th>Mean interval from initiation of Tx to occurrence of adverse effect, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>5 (8,3)</td>
<td>6,4</td>
</tr>
<tr>
<td>Arthralgias/arthritis</td>
<td>4 (6,7)</td>
<td>7,8</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>4 (6,7)</td>
<td>13,8</td>
</tr>
<tr>
<td>Renal toxicity</td>
<td>2 (3,3)</td>
<td>14,5</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>1 (1,7)</td>
<td>3</td>
</tr>
<tr>
<td>Severe gastritis</td>
<td>1 (1,7)</td>
<td>1</td>
</tr>
</tbody>
</table>
Adverse events by causing drug for 152 (85 adverse events) MDR-TB patients

- **Z (2)**
- **Km (3)**
- **Cm (5)**
- **Pro (10)**
- **Ofl (3)**
- **PAS (9)**
- **H+T (21)**

- **Hepatitis**
- **Hearing loss**
- **Renal failure**
- **Hepatitis**
- **Stevens-Johnson**
- **Visual disturbances**
- **Peptic ulcer**
- **Leucopenia**
- **Hair loss**
- **Severe diarrhea**
- **Vomitus**
- **Anemia**

- **Z (2)**
- **Km (3)**
- **Cm (5)**
- **Pro (10)**
- **Ofl (3)**
- **PAS (9)**
- **H+T (21)**

- **Hepatitis**
- **Hearing loss**
- **Renal failure**
- **Hepatitis**
- **Stevens-Johnson**
- **Visual disturbances**
- **Peptic ulcer**
- **Leucopenia**
- **Hair loss**
- **Severe diarrhea**
- **Vomitus**
- **Anemia**
Conclusions

- Management of adverse effects is an important part of DOTS Plus program. It includes:
  - Training and education
  - Monitoring and registration of side effects
  - Proper management if side effects occur
  - Psychosocial support for patients
  - Ancillary drugs