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The side-effects of TB therapy

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Educational aims

To provide up-to-date insights on:
- the side-effects of anti-TB chemotherapy
- the symptom-based approach to the management of side-effects
- the influence of side-effects on the outcomes of anti-TB treatment.

Summary

There is still much debate concerning the frequency and severity of symptoms of TB when undergoing chemotherapy. In addition, the frequency of complications is hard to quantify as many patients are treated with a range of different drugs. However, this article aims to give a brief overview of the side-effects associated with anti-TB drugs and the most appropriate management approaches to take.

It has been suggested that only a minority of patients successfully complete their full course of anti-tuberculosis (TB) chemotherapy without significant side-effects. There is also an opposing view that most patients with TB complete their treatment without serious adverse effects. What is the truth? Modern anti-TB chemotherapy regimens have been in use for >30 years. However, the frequency of severe complications is not well known, probably due to lack of notification and under-reporting. It is clear that many patients have adverse reactions which complicate treatment and have an influence on treatment outcomes. However, it is difficult to measure the efficacy or toxicity of a particular drug, since anti-TB drugs are usually administered in combination regimens of several drugs. Therefore, any care provider treating a TB patient is assuming a public health function that includes not only prescribing an appropriate regimen, but also ensuring adherence to the regimen and monitoring of the treatment, including the side-effects of drugs until treatment is completed.

Glossary

Amk:	Amikacin
Cm:	Capreomicin
Cs:	Cycloserine
E:	Ethambutol
H:	Isoniazid
Et:	Ethionamide (Prothionamide)
Km:	Kanamycin
O:	Ofloxacin
Pas:	Para-aminosalicylic acid
R:	Rifampicin
S:	Streptomycin
Tha:	Thioacetazon
Z:	Pyrazinamide

Table 1 Adverse effects of essential anti-TB drugs

Drug	Main effects	Rare effects
H	Peripheral neuropathy Skin rash Hepatitis[f] Sleepiness and lethargy	Convulsions Psychosis Arthralgia Anaemia
R[#]	Gastrointestinal: abdominal pain, nausea, vomiting Hepatitis Generalised cutaneous reactions Thrombocytopenic purpura	Osteomalacia Pseudomembranous colitis Pseudoadrenal crisis Acute renal failure Haemolytic anaemia
Z[¶]	Arthralgia Hepatitis Gastrointestinal	Cutaneous reactions Sideroblastic anaemia
E[+]	Retrobulbar neuritis	Generalised cutaneous reactions Arthralgia Peripheral neuropathy Hepatitis (very rare)
S[§]	Vestibular and auditory nerve damage Renal damage Cutaneous hypersensitivity	Pain, rash, induration at injection site Numbness around the mouth and tingling soon after the injection
Tha	Skin rash, sometimes with mucosal involvement	Acute hepatic failure Exfoliative dermatitis[##]

[#]: risk increases with intermittent regimens or large intervals between regimens; [¶]: most hepatotoxic; [+]: contraindicated for young children who cannot be tested for impaired visual acuity; [§]: contraindicated in pregnant women and patients with myasthenia gravis; [f]: most frequent in adults >35 years and can be fatal; [##]: many be more common and fatal in HIV-infected patients and, therefore, Tha is contraindicated.

Table 2 Adverse effects of reserve anti-TB drugs

Drug	Main effects	Rare effects
Km[#] Am[#] Cm[#]	Vestibular (vertigo) and auditory nerve damage Nephrotoxicity	Cutaneous hypersensitivity Clinical renal failure
Et[#]	Gastrointestinal: anorexia, nausea, diarrhoea, abdominal pain Hepatotoxicity[§]	Convulsion Mental symptoms Impotence Gynaecomastia
Fluoroquinolones[#,¶]	Gastrointestinal: anorexia, nausea, vomiting	Anxiety Dizziness Headache Convulsion Rupture of the Achilles tendon
Cs[+]	Dizziness Headache Depression Psychosis Convulsion	Suicide Generalised hypersensitivity Hepatitis
Pas[+]	Gastrointestinal: anorexia, nausea, vomiting Hypersensitivity reactions (fever, rash, pruritus)	Hypothyroidism Haematological reactions

[#]: contraindicated in pregnant women; [¶]: contraindicated in growing children; [+]: should be avoided in patients with epilepsy, mental illness and alcoholism; [§]: patients with diabetes, liver disease, alcoholism or mental disease should be carefully monitored.

Adverse effects of anti-TB drugs

Essential anti-TB drugs are those used in as first-line therapy. The adverse effects of essential anti-TB drugs are given in table 1.

Reserve anti-TB drugs are those used in 2nd-line (drug-resistant TB) treatment. The adverse effects of reserve anti-TB drugs are given in table 2.

What to do if symptoms of adverse effects occur

If symptoms of adverse effects occur the following should be done:

- the dose of drugs should be checked
- all other causes of symptoms should be excluded
- the seriousness of the adverse effects should be estimated
- the adverse effects should be registered
- the drugs should eventually be reintroduced gradually when symptoms disappear
- the development of drug resistance should be avoided.

Symptom-based approach to the management of adverse effects

The following tables give a brief description of how adverse effects should be managed when the effect are minor (table 3) and major (table 4).

Management of hepatotoxicity

Hepatotoxicity is the most common cause of iatrogenic disease in TB treatment. Anti-TB drugs can induce various degrees of hepatotoxicity, from a transitory asymptomatic rise in transaminases (which in extreme cases may lead to interruption of TB treatment), to acute liver failure (ALF) (when hepatic encephalopathy occurs and prothrombine time is <50%, usually leading to the need for liver transplantation or even death). The frequency of hepatotoxicity in different countries varies 1–10%.

Hepatotoxicity due to isoniazid is most common, as isoniazid has been used for TB treatment (both latent and active TB) since 1952. However, pyrazinamide is the most hepatotoxic among essential anti-TB drugs, in particular at doses of >30 mg per kg per day. Rifampicin has a low hepatotoxicity. However, due to its enzyme-

Table 3 Symptom-based approach to the management of minor adverse effects: continue anti-TB drugs

Adverse effects	*Drug*	*Management*
Anorexia, nausea, abdominal pain	*R, Z, Et, O, Pas*	*Small meals or last thing at night*
Arthralgia	*Z, (H, E), O*	*Aspirin*
Burning in the feet	*H*	*Pyridoxine 100 mg*
Orange/red urine	*R*	*Reassurance (explanation)*

Table 4 Symptom-based approach to the management of major adverse effects: stop anti-TB drugs

Adverse effects	Drug	Management
Deafness (no wax on auroscopy)	S, Km, Amk, Cm	Use E
Dizziness	S, Km, Amk, Cm, O	Use E
Jaundice hepatitis (other causes excluded)	H, Z, R, Tha, E, Et, Cs, Pas	Re-introduce drugs grouped serially while monitoring liver function, with most likely agent introduced last
Itching, skin rash	Tha, S, H, R, Z, Pas	Antihistamines, steroids
Vomiting/confusion	Suspect drug-induced hepatitis	Urgent liver function tests and prothrombin time
Visual impairment (other causes excluded)	E	Visual examination
Shock, purpura, acute renal failure	R, S, Km, Amk	Use different combinations of drugs

inducer effect it may increase the toxicity of isoniazid when the two drugs are combined.

Mild hepatotoxicity (a rise in transaminases of 3–5 times the normal level) does not require any modification in treatment, only more frequent visits and laboratory tests. In cases of moderate hepatotoxicity (a rise in transaminases of between 3–5 and 10 times the normal level), chemotherapy should be stopped as soon as possible, controlling for the risk of ALF should be started and patients should be hospitalised if necessary. However, the risk of ALF is low.

Severe hepatotoxicity (a rise in transaminases >10 times the normal level) occurs in one out of every 1,000 cases treated, and is associated with a high fatality rate of ~2.5%. Hepatitis is the usual clinical manifestation at this degree of toxicity and the risk of ALF is high. Spontaneous survival after ALF is <10%. The only treatment that increases survival is liver transplantation (survival rates >80%).

Table 5 Management of severe rash: reintroduction of anti-TB drugs

Day	Drug	Dose
1	H	50 mg
2	H	300 mg
3	RH	1/2 tablet
4	RH	1 tablet
5	RH	Full dose
6	RH+Z	Day 5 dose + 1/2 tablet
7	RH+Z	Day 5 dose + 1 tablet
8	RH+Z	Full dose
9	RH+Z+E	Day 8 dose + 1/2 tablet
10	RH+Z+E	Day 8 dose + 1 tablet
11	RH+Z+E	Full dose
12	RH+Z+E	Full dose

Management of severe rash: reintroduction of anti-TB drugs

Itching/skin rash is also a very common major adverse effect of anti-TB chemotherapy, which requires a quick response. Table 5 provides a guide to how a patient should be managed in this situation.

Life-threatening adverse effects

Life-threatening adverse effects include anaphylaxis, severe toxic, allergic reactions (exfoliative dermatitis, syndrome Steewen-Johnson), severe gastritis with bleeding, severe hepatitis and renal failure. In such circumstances, treatment must be stopped. If the offending drug is unknown then all drugs must be continued and the emergency department contacted.

The influence of side-effects on the outcomes of anti-TB treatment

One concern when considering side-effects is whether they prevent patients from taking medication and, hence, influence the outcomes of anti-TB treatment. In the cohort year of 2002, the global success rate of treatment with standardised anti-TB chemotherapy with 1st-line drugs was 82% and the WHO European region success rate was 76% [1]. In the results from five DOTS-plus projects (Estonia, Latvia, Orel, Philippines and Tomsk), only 2% of 924 patients stopped treatment, although 30% did require removal of the suspected drug from the regime due to adverse effects. The five most-common reported effects included: nausea/vomiting (32.8%), diarrhoea (21.1%), arthralgia (16.4%), dizziness/vertigo (14.3%) and hearing disturbances (12.0%) [2]. Hence, side-effects of anti-TB chemotherapy need not necessarily adversely effect outcomes.

Conclusions

In conclusion, the main adverse effects of anti-TB drugs usually occur during the first 2–3 weeks of treatment. If these side-effects are not recognised on time and managed properly they can lead to treatment interruption or can even can be life threatening. Proper monitoring has to be carried out during the whole treatment course, including patient education, clinical examination, laboratory tests, *etc.*

Adverse effects are manageable in TB treatment provided that appropriate management approaches are applied, including altering dosages when appropriate, ancillary drugs to treat adverse events, discontinuation of drugs if needed, special training for staff on adverse events and standard protocols for registration. A patient-centred, individualised approach to treatment support is a core element of all TB control efforts.

Educational questions

Which of the following statements are correct?

1. Anti-TB drugs have the following side-effects
a) All. b) None. c) Few. d) Many.
2. This drug is contraindicated in young children:
a) Isoniazid. b) Pyrazinamide. c) Ethambutol. d) Ofloxacin.
3. This drug is contraindicated in pregnant women:
a) Streptomycin. b) Cycloserin. c) Ethionamide. d) Rifampicin.
4. This drug is contraindicated for HIV/AIDS patients:
a) Rifampicin. b) Thioacetazon. c) Ethionamide. d) Pas.
5. Minor adverse effects include:
a) Deafness. b) Anorexia and other gastrointestinal symptoms. c) Jaundice. d) Neither a, b or c.
6. Major adverse effects include:
a) Arthralgia. b) Orange/red urine. c) Nausea. d) Dizziness.
7. Severe hepatotoxicity occurs if there is a rise in transaminases:
a) >10 times the normal level. b) 3–5 times the normal level.
c) From 3–5 to 10 times the normal level. d) Does not depend on the rise in transaminases.
8. Severe hepatotoxicity is associated with:
a) Low mortality rate. b) High mortality rate. c) Acute liver failure. d) Neither a, b or c.
9. Life-threatening adverse effects include:
a) Abdominal pain. b) Burning in the feet. c) Exfoliative dermatitis. d) Renal failure.
10. Most of adverse effects of anti-TB drugs are:
a) Manageable. b) Irreversible. c) Life threatening. d) Incurable.
11. Adverse effects of anti-TB drugs can be life threatening:
a) Never. b) If they are not managed properly. c) During the first 2–3 weeks. d) If caused by reserved drugs.

Suggested further reading

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1. *World Health Organization Report 2005. Global Tuberculosis Control. Geneva, Switzerland, World Health Organization, WHO/HTM/TB/2005.349.*
2. *Stop TB Working Group on DOTS-Plus for MDR-TB. Paris, France, WHO, 2003.*

Suggested answers

1. a
2. c
3. a and c
4. b
5. b
6. d
7. a
8. b and c
9. c and d
10. a
11. b