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TB CARE II



ADVERSE EFFECTS AND ADHERENCE TO MDR-TB TREATMENT IN CHILDREN

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**Friday
June 6, 2014**

**9:00 a.m. EDT
(GMT -5:00)**

www.drtnetwork.org

Objectives

- By the end of the session you should be able to:
 - List the adverse effects associated with MDR-TB treatment in children
 - Describe an approach for routine monitoring for adverse effects
 - Describe the management of the most frequent clinically relevant adverse effects

Introduction

- Assessing adverse effects (AEs) in children is more difficult in children than in adults
- Overall, AEs are less frequent than in adults
- Baseline assessment for some AEs is important, as problems may exist before start of treatment (e.g. hearing assessment, thyroid function tests)
- Limit AEs by prescribing and dispensing the correct dosage of each drug
- Not all AEs are serious and few require considering stopping or changing of drugs
- Some AEs are common and occur with many drugs (e.g. skin rashes, nausea and vomiting)

MDR-TB Weight-Based Dosing Chart for Children

Target Dose	Group 1: Oral first-line anti-TB drugs				Group 2: injectable anti-TB drugs (injectable agents or parental agents)	Group 3: Fluoroquinolones				Group 4: Oral bacteriostatis agents				Group 5:		Target Dose																								
	Ethambutol (15-25 mg/kg)		Pyrazinamide (30-40 mg/kg)			Levofloxacin (15-20 mg/kg)		Moxifloxacin (7.5-10 mg/kg)		Ofloxacin (15-20 mg/kg)		Cycloserine/Terizidone (15-20 mg/kg)		PAS (150-200 mg/kg)			Prothionamide/Ethionamide (15-20 mg/kg)	Isoniazid High Dose (15-20 mg/kg)																						
Available Formulations	100 mg tablet	Suspend 400mg tab in 8 mL of water for a 50 mg/mL suspension	400 mg tablet	500 mg tablet		250 mg tablet	25 mg/mL suspension	400 mg tablet	20 mg/mL suspension	300 mg tablet	250 mg capsule	1 capsule in 10 mL water	Daily	Twice Daily	250 mg tablet	100 mg tablet																								
Wt (kg)	Consult with a clinician experienced in pediatric MDR-TB prescribing for neonates (<28 days of age) and infants weighing <3 kg																Wt (kg)																							
<3																	<3																							
3-3.9	1 tab	2 mL	.25 tab	.25 tab	To illustrate dose calculation, take the example of a child that weighs 6.9 kg. Both the low and high doses for the child's weight are calculated. For Kanamycin: Low dose: 15 mg/kg x 6.9 kg = 103 mg. High dose: 30 mg/kg x 6.9 kg = 207 mg. A convenient dosing is then chosen between the two numbers. Select a dose between the two numbers and towards the higher number. In this case, choose: 200 mg per day, single dose. Calculate the number of mL to draw up on the syringe based on the mg/mL concentration of the preparation.	.25 tab	2.5 mL	not recommended	1.5 mL	.5 tab	.25 cap	2.5 mL	500 mg	250 mg	.25 tab	Group 5 drugs are not recommended by the WHO for routine use in MDR-TB treatment because their contribution to the efficacy of MDR regimens is unclear. Their role in pediatric MDR-TB treatment is even less clear. Most of these drugs are expensive, and some require intravenous administration, and/or have severe side effects. However, they can be used in cases where adequate regimens are impossible to design with the medications from Group 1-4. They should be used in consultation with an expert in the treatment of DR-TB.	.5 tab	3-3.9																						
4-4.9			.5 tab	5.0 mL		2.5 mL	.5 cap		5 mL		1000 mg	500 mg	.5 tab	4-4.9																										
5-5.9			2 tabs	4 mL		.5 tab	.5 tab		.75 tab		7.5 mL	5 mL	1 tab	.75 cap	7.5 mL		2000 mg	1000 mg	.75 tab	1 tab	1500 mg	750 mg	1 tab	5-5.9																
6-6.9																								3 tabs	6 mL	1 tab	1 tab	1 tab	10 mL	1 cap	1 cap	2500 mg	1250 mg	1 tab	3 tabs	1 tab	1500 mg	750 mg	1 tab	6-6.9
7-7.9																																								7-7.9
8-8.9	4 tabs	8 mL	1.5 tabs	1.5 tabs	1.5 tabs	15 mL	.5 tab	7.5 mL	1.5 tabs	1.5 caps	15 caps	3000 mg	1500 mg	1.5 tabs	3 tabs	4000 mg	2000 mg	1.5 tabs	8-8.9																					
9-9.9			5 tabs																10 mL	2.5 tabs	2 tabs	2 tabs	20 mL	2 tabs	2 tabs	2 caps	20 mL	5000 mg	5000 mg	2 tabs	5 tabs	6000 mg	6000 mg	2 tabs	9-9.9					
10-10.9																																			10-10.9					
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For preventive regimens, consult with experts regarding optimal regimen construction. The doses of isoniazid, ethambutol, and fluoroquinolones for preventive regimens are the same as in this dosing chart.



Group 2	Streptomycin	Arikacin	Kanamycin	Capreomycin
Daily Dose	25-40 mg/kg once daily	15-20 mg/kg once daily	15-20 mg/kg once daily	15-20 mg/kg once daily
Maximum Daily Dose	1000 mg	1000 mg	1000 mg	1000 mg

Group 5	Cladribine (CDF)	Amoxicillin-clavulanate (AMC-CLV)	Meropenem (MPM)	Linezolid (LZO)	Clarithromycin (CLR)
Daily Dose	3-5 mg/kg once daily if the child has <25kg, give 100mg every second day	60 mg/kg in two divided doses based on the amoxicillin component	20-40 mg/kg IV every 8 hours	10 mg/kg dose twice daily for children <10 years of age 300 mg daily for children >10 years of age (also give vitamin B6)	7.5 mg/kg twice daily
Maximum Daily Dose	200 mg	4000 mg amoxicillin and 500 mg clavulanate	8000 mg	600 mg	1000 mg

Chart developed by
Chelsea GawnMark

<http://sentinel-project.org/treatment-guidance/>

WHO Drug groups in MDR-TB treatment

- Group 1: 1st-line drugs – INH, RIF, EMB, PZA
- Group 2: 2nd-line injectable drugs: kanamycin, amikacin or capreomycin
- Group 3: The fluoroquinolones – OFX, LFX or MFX. Best of 2nd-line drug available
- Group 4: Oral 2nd-line drugs:
 - Ethionamide/prothionamide (*inhA* mutation?)
 - Cycloserine / Terizidone
 - PAS (para-aminosalicylic acid)
- Group 5: Uncertain efficacy
 - high-dose INH – if low-level INH resistance (or *inhA* promoter region mutation)
 - linezolid, clofazimine and possibly some others



REVIEW

Paediatric use of second-line anti-tuberculosis agents: A review

James A. Seddon^{a,b,*}, Anneke C. Hesseling^a, Ben J. Marais^c, Helen McIlleron^d, Charles A. Peloquin^e, Peter R. Donald^f, H. Simon Schaaf^{a,f}



Damien Schumann

Tuberculosis. 2012; 92: 9-17

Group 1 – First-line drugs

- Ethambutol and pyrazinamide often still used in MDR-TB treatment.
- Ethambutol
 - Optic neuritis:
Vision acuity and colour vision (reversible if stopped early)
 - Use with caution in patients with renal impairment
- Pyrazinamide
 - Hepatotoxicity
 - Arthralgia (very rare – may be more if used with FQNs)
 - Skin rashes/photosensitivity



Group 2 – 2nd-line injectables

- All have similar AEs (Km, Am, Cm)
- Nephrotoxicity and electrolyte disturbances (Potassium) – uncommon in children
- Ototoxicity: Hearing loss most common
 - Up to 50% in adults and 25% in children
 - Sensorineural
 - High frequency hearing loss most common
 - Can be acute with severe hearing loss
 - Some genetic markers, but these are uncommon
 - HL may continue after stopping the drug
 - Vestibular (balance/tinnitus) not well studied in children

Group 2 – 2nd-line injectables (cont.)

Ototoxicity (cont.)

- How to assess
 - Pure tone audiometry
 - Otoacoustic Emission (OAE) (ensure can test high frequencies)
- Assess middle ear via tympanometry or otoscopy (conductive hearing loss)
 - Interpret OAE/pure tone in light of these results.
- Routinely screen for hearing abnormality
 - Cannot rely on subjective report of hearing loss or gross evidence of hearing loss
 - Baseline, then monthly
 - If abnormal then more frequent

Hearing loss in children treated for multidrug-resistant tuberculosis

James A. Seddon ^{a,b,*}, Stephanie Thee ^c, Kayleen Jacobs ^d, Adam Ebrahim ^d, Anneke C. Hesselink ^a, H. Simon Schaaf ^{a,e}

Known complication of aminoglycosides/polypeptides
Difficult to evaluate especially in young children

In a recent retrospective study we found 24% definite hearing loss amongst 94 children evaluated (either by pure tone audiometry or by otoacoustic emissions – depending on age and cooperation of the child)

Seddon et al; J Infect 2012



Case 1

- 3-yr-old girl with confirmed MDR-TB and extensive pulmonary infiltrates.
- On treatment hd-INH, PZA, ETO, TZD, LFX, EMB and AM (injectable) – now month 3 and 2nd culture at month 1 still positive
- Otoacoustic Emission (OAE) demonstrate high-frequency HL at 6000-8000 Hz bilaterally. Baseline OAE was normal.
- No other AEs of importance found
- How are you going to manage this case?

Question 1: How are you going to manage this case?

- 1) Tell the mother child is better off deaf than dead
- 2) See if there is an alternative drug available to exchange with amikacin, e.g. PAS or linezolid
- 3) Stop amikacin injections irrespective of culture results or improvement of child's TB
- 4) Continue amikacin injections irrespective of culture results or improvement of child's TB
- 5) None of the above

Case 1 - discussion

- Better deaf than dead? Not ideal either way!
- Look at clinical progress of the child, did the CXR improve markedly? Any negative culture results now at month 2?
- Are there any other “good” anti-TB drugs available, e.g. PAS or linezolid?
- Are 2nd-line DSTs available – not FQN resistant or already 2nd-line injectable resistance?
- Re-evaluate hearing in 2 weeks – same or worse?
- Consider stopping injectable drug if: good improvement and another drug available and no 2nd-line DST resistance. Individualise EACH CASE

Group 3 - Fluoroquinolones

- Far fewer AEs than originally anticipated!!!
- Arthralgia/arthritis – very rare (tendon rupture adults)
- Neurological AEs have been described
 - Insomnia (sleeplessness)
 - Hallucinations (overdose)
 - Headache, dizziness, drowsiness
- GIT disturbances
 - Abdominal pain, nausea, vomiting
- QT prolongation
 - Not yet documented in children. Mainly moxifloxacin
 - Not necessary to screen or monitor with ECGs

Group 4 – Oral 2nd-line drugs

- Ethionamide/prothionamide
 - GIT disturbances – metallic taste, nausea, vomiting
Vomiting: May need to split dose or start with lower dose, but usually stops within 1-2 weeks
 - Hepatotoxicity
 - Very rare: convulsions, peripheral neuropathy – pyridoxine responsive
 - Gynaecomastia may occur
 - Diabetes may be difficult to control when starting ethionamide

Abnormal thyroid function tests in children on ethionamide treatment

S. Thee,^{*†} E. W. Zöllner,[‡] M. Willemse,[§] A. C. Hesselning,[†] K. Magdorf,[†] H. S. Schaaf[†]

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In a retrospective study of 137 children on a regimen containing ethionamide:

Abnormal TFTs were recorded in 79 (58%) children

Elevated serum TSH and suppressed fT4 in 30 (22%)

The risk for hypothyroidism was higher on regimens including PAS and in HIV-infected children.

Thee et al; IJTLD 2011

Group 4 – Oral 2nd-line drugs

- Ethionamide/prothionamide (cont.)
 - Hypothyroidism – do routine thyroid function tests (TSH & fT4) 2-monthly.
 - Symptomatic hypothyroidism uncommon
 - Interpret with caution in first 1-2 months of treatment - acute illness may affect TFTs
 - If primary hypothyroidism (elevated TSH, low fT4), supplement with levothyroxine
 - Hypothyroidism reversible - stop levothyroxine once ETO/PAS stopped

Group 4 – Oral 2nd-line drugs

- Cycloserine/Terizidone
 - Neurological system AEs: Dose-related anxiety, confusion, depression, psychosis also other like convulsions
 - Pyridoxine supplementation should be prescribed
 - Neurological AEs rare in children
 - Reduce the dose or stop the drug if CNS AEs occur

Group 4 – Oral 2nd-line drugs

PAS

- GIT disturbances
 - Anorexia, diarrhoea, nausea
- Hypothyroidism
 - Increased risk with ethionamide
- Hepatotoxicity

Case 2

- A 4-yr-old boy on pre-XDR-TB treatment presents with new onset vomiting after 2 months of treatment. Treatment is hd-INH, PZA, EMB, ETO, TZD, LFX, CM & PAS – also on pyridoxine. He is HIV-negative. Although he vomited a few times when he started treatment, this had stopped after one week on treatment. On examination he has no skin rash, no neck stiffness, no diarrhoea, but looks slightly jaundiced with a palpable liver edge
- **Diagnosis? How would you manage this child?**

Question 2: How would you manage this child?

- 1) Stop all hepatotoxic drugs immediately
- 2) Do screening for viral hepatitis
- 3) Do liver enzyme levels and total/conjugated BR
- 4) Do abdominal ultrasound if conjugated hyperbilirubinaemia
- 5) Reintroduce essential drugs one by one once liver enzymes have normalised
- 6) None of the above
- 7) All of the above

Case 2 - Discussion

- Hepatitis/Hepatotoxicity
- Signs of hepatotoxicity: new onset vomiting, abdominal pain, jaundice (late)
- Stop all liver-toxic drugs (INH, PZA, ETH, PAS)
- Do liver function tests incl. ALT, AST, total and conj BR. Do abdominal ultrasound if obstructive jaundice suspected (nodal compression)
- Screen for Hepatitis A, C and others as indicated
- Wait until liver enzymes normalise – restart essential drugs one by one checking ALT mainly

Group 5 – Drugs with uncertain efficacy

- High-dose INH: (15-20mg/kg max dose 400mg)
 - May still have effect in low-level INH resistance (either MIC or inhA mutation conferring resistance)
 - Hepatotoxicity
 - Peripheral neuropathy (Pyridoxine supplementation)
- Clofazimine: (Dosing difficult in children)
 - Can cause red colour of urine, faeces, sweat and red-brown (dark) pigmentation of the skin, conjunctiva & cornea
 - GIT: diarrhoea, nausea, vomiting
 - Skin rashes
 - QT prolongation?

Group 5 – Drugs with uncertain efficacy

- Linezolid (effective drug, very expensive still)
 - Myelosuppression (anaemia, leucocytosis, thrombocytopenia)
 - Peripheral neuropathy (optic neuritis)
 - Pancreatitis
 - Lactic acidosis
 - All of the above rare at currently recommended lower dosages in children (10mg/kg twice daily <10 yrs of age and 300mg/day 10-13 yrs of age)

Case 3

- A 4-yr-old girl with MDR-TB and recently diagnosed HIV infection. She was first started on MDR-TB treatment (PZA, ETO, EMB, TZD, LFX, AM) and 2 weeks later on ARVs (ABC, 3TC & EVF). Also on co-trimoxazole, pyridoxine and vit B Co.
- One month later she presents with severe maculo-papular skin rash, fever and general malaise
- How would you manage this child?

Case 3 - Discussion

- Exclude other causes such as intercurrent infection (viral, bacterial?).
- Drug adverse effect? Many drugs may cause drug rash – in this case co-trimoxazole, EFV, 3TC (NVP also often a cause). ABC can cause hypersensitivity reaction – usually soon after onset of treatment. Almost all anti-TB drugs can cause some kind of skin rash.
- If not severe, can continue drugs and follow up. Watch out for Stevens Johnson syndrome, hypersensitivity reactions. In severe cases of skin rash – stop all drugs.
- Reintroduce anti-TB drugs least likely to cause skin rash, thereafter ARVs. Often exclude co-trimoxazole as common cause of drug AEs.

Possible routine monitoring tests

- Hepatotoxic drugs: ALT – not routinely indicated, although some institutions may require this
- Injectables drugs:
 - Baseline & Monthly hearing screening while on injectables and 6 months after completion.
 - Creatinine and K+ at baseline & 2-monthly while on injectables
- Ethionamide/PAS: Thyroid function tests at baseline and 2-monthly
- Linezolid: Initial monthly FBC – later 2-monthly

Adherence (and support)

- Treatment in hospital and in community needs to be observed – children are ingenious when it comes to making plans how NOT to take their treatment!
- Poor palatability of meds may contribute to adherence problems in some
- Ask children/caregivers to identify the tablets/capsules and how many of each are taken – can check on dosage
- Phone the clinics who dispense the treatment – do they collect the drugs regularly or is there DOT?
- Pill counts and other methods may be used
- Most important: identify a reliable caregiver to provide the drugs and observe the child taking it



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Adherence (and support)

- Monitor adverse effects and address these, as could lead to defaulting treatment
- Teenagers – notoriously difficult group to adhere to treatment: Communication (clinic staff) and peer pressure (stigma/mockery) – both common problems
- Nutritional support and financial support often required by families – especially if caregivers/parents also ill

Conclusion

- Important to know adverse effects of the drugs used for MDR-TB treatment
- Monitor routinely for most frequent and most important AEs
- Hearing loss most frequent severe AE, and should be actively assessed
- Adherence support crucial to successful outcome

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