NTM treatment:
Pharmacological challenges

Isabel Spriet

Pharmacy Dpt. UZ Leuven &
Department of Pharmaceutical and
Pharmacological Sciences, KU Leuven

Isabel.Spriet@uzleuven.be

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Société belge d'infectiologie et de microbiologie clinique
Belgische vereniging voor infectiologie en klinische microbiologie

Disclaimer

- I am not a NTM specialist

…. so bringing the pharmacological challenges is also challenging…

- What follows is based on

Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline
Daley CL et al. Clin Infectious Dis 2020; 71: e1-e36.

https://www.ntmfacts.com/treat/
www.farmacotherapeutischkompas.nl

MAC treatment

INITIAL TREATMENT	*Macrolide susceptible cases*	
	Non-cavitary nodular bronchiectatic disease 3x/WEEK	**Cavitary or severe bronchiectatic disease DAILY**
	Azithromycin 500 mg	**Azithromycin 250 – 500 mg**
	Rifampicin 600 mg	**Rifampicin 10 mg/kg (450 or 600 mg)**
	Ethambutol 25 mg/kg	**Ethambutol 15 mg/kg**
		Amikacin IV 15 mg/kg/day, if susceptibility has been documented

- In case of drug intolerance: clofazimine (100 mg/day) or moxifloxacine (400 mg/day) might be used as alternatives
- Treatment duration: 12 months after sputum culture conversion

Macrolides

- Cornerstone of MAC treatment if susceptibility has been documented
- Azithromycin (Zitromax) is preferred over clarithromycin
  - Equal efficacy, but better tolerance
  - Single daily dose → lower pill burden
  - No dose adjustment in patients with renal insufficiency
  - Less DDI
  - QTc prolongation
- Clarithromycin (Biclar) (2 x 500 mg/day) can be used as alternative if azithromycin is not well tolerated (or when azithro is not available)
  - Less well tolerated because of metallic or bitter taste, diarrhea, nausea, loss of appetite
  - Dose adjustment to 2 x 250 mg/day when eGFR < 30 mL/min
  - Potent CYP450 inhibitor - more frequently involved in DDI
  - QTc prolongation
- Given in a 3-drug combination, with ethambutol and rifampicine, to prevent acquired macrolide resistance

Rifamycins

- Rifampicine (Rifadine, caps 150 and 300 mg) is preferred over rifabutin
  - Better tolerance
  - Should be taken on empty stomach, if not well tolerated: intake with food
  - Hepatotoxicity (mainly cholestatic pattern), use with caution in patients with hepatic impairment
  - Orange-red discoloration urine, contact lenses
  - Might be challenging in case of DDIs
    - Very strong CYP450 inducer
    - Contra-indicated with tacrolimus, ciclosporine, voriconazole, isavuconazole

- Rifabutin (Mycobutin) can be used as alternative, in case of DDI or hepatotoxicity
  - 150 – 300 mg/day, max. 150 mg/day when combined with clarithromycin
  - Reduce dose to 150 mg/day when eGFR < 30 mL/min
  - Might lead to uveitis

Ethambutol

- Available as 400 mg tablets (Myambutol) and 1g vials (EMB-Fatol, via import)
- Dosing:
  - daily regimen: 15 mg/kg
  - thrice weekly: 25 mg/kg
  - max. 1600 mg/day, can be taken with or without food

- AE:
  - optic neuritis with vision changes (blurry vision, and difficult red-green discrimination)
  - peripheral neuropathy (with tingling in hand and feet)

- DDI: absorption is decreased when ethambutol is taken with aluminium – containing antacids
  - if antacids are combined, take into account interval of at least 4h before administering ethambutol

Amikacin - parenteral

- Amikacine is typically added in patients with severe, cavitary disease if MIC < 64 mg/L
- Available as IV solution 500 mg/100 mL and 1g/100 mL (Amikacine Bbraun or Fresenius), and recently also again as Amikacin 500 mg/2 mL (for inhalation)
- Dosing:
  - Recommended starting dose: 15 mg/kg, be cautious in patients with eGFR < 60 mL/min
  - Maintenance dosing based on TDM
    - For renal and otoxicity: Cmin < 5 mg/L
    - For efficacy: targets are less clear: Cmax: 35-45 mg/L (daily dosing) or 65-80 mg/L (thrice weekly dosing)
- Duration: 8-12 weeks
  - When duration > 15 weeks, up to 30% of ototoxicity has been reported
  - Baseline audiogram is recommended
  - Muscle weakness has also been reported
- *Streptomycin IV 10-15 mg/kg is recommended in NTM guidelines as an alternative for amikacin*
  - *Not available in Belgium – vials 1g can be imported*
  - *However, assay is not available for TDM*

Amikacin - inhalation

- Inhaled amikacin: 250 – 500 mg/day, 3-7 times per week
  - Previously carried out with Likacin, 500 mg 2 mL (via import) – 8,37 €/ amp (non-reimbursed)
  - Since recently: Amukin 500 mg/2 mL again available (reimbursed)
  - Not easy to administer (very sticky), and not well tolerated

- ALIS: amikacin liposomal inhalation suspension – 590 mg/8,4 mL once daily, is recommended in patients with refractory disease after 6 months of intial therapy
  - ALIS is approved by FDA in treatment of refractory MAC
  - Arikayce is approved by EMA as orphan drug in 2014 - limited availability in Belgium via CUP program (monitored NTM consilium)
  - Expected to be available in near future for non-CF refractory MAC lung disease

Clofazimine

- Available as Lamprene tablets, 50 mg or 100 mg via import
- Previously used to treat leprosy (*M. leprae*), now increasingly used in drug resistant MAC where standard therapy fails
- Dose: 100 – 200 mg/day
- No dose adjustments, but use with caution in hepatic impairment
- Main AEs:
  - Gastro-intestinal: loss of appetite; diarrhea; abdominal pain
  - Anticholinergic: Skin: dry skin; pink, red, orange or brown skin discoloration (up till months after stopping treatment)

Treatment of other NTM

	M. abscessus
Treatment based on susceptibility testing?	Yes, Macrolides Amikacin
Regimen	**At least 3 (active) drugs:** - **Parenteral amikacin** - **Macrolides** - **Clofazimine** - **Imipenem or cefoxitin** - **Tigecyline** - **Linezolid** In patients with *M. abscessus* strains with macrolide resistance, azithromycin can be continued for its **immunomodulatory properties** but should **not** be counted as an active drug in the multidrug regimen.
Duration	No optimum duration defined, determined on case by case basis

Treatment of other NTM – parenteral

Imipenem-cilastatine

- Available via import (Imipenem Cilastatine Aurobindo, via 500/500 mg 20 mL)
- Carbapenem + cilastatine inhibits renal dehydropeptidase-1, which inactivates imipenem
- **Dose:** 500 – 1000 mg 2-3x/day
- Dose should be adapted in renal insufficiency
- **Main AE:** neurotoxicity, use in combination with other proconvulsant drugs
- **DDI:** imipenem will lead to a decrease in valproic acid concentrations, necessitating alternative anti-epileptic treatment

Tigecycline

- Available as Tygacil 50 mg vials
- Tetracycline
- **Dose:** 25 – 50 mg 1-2x/day (once daily dosing is better tolerated)
- Dose should be adapted in hepatic impairment to 25 mg 1-2x/day

- **Main AE:** nausea and vomiting

Cefoxitin

- Available via import (Cefoxitin vials of 1g or 2g)
- **Dose:** 2-4g, 2-3x/day (max 12g/day)
- Dose should be adjusted in renal insufficiency

- **Main AE:** IgE mediated allergy, liver function abnormalities

Treatment of other NTM – oral

Linezolid

- Available as tablets, syrup and infusion bags
- **Dose:** 600 mg, 1-2x/day (once daily dosing is better tolerated)
- No dose adjustments
- **Main AEs:**
  - bone marrow suppression, with thrombopenia, neutropenia, pancytopenia
  - peripheral neuropathy (tingling, numbness in hand and feet) and optic neuritis, associated with longterm treatment
  - lactic acidosis (mitochondrial dysfunction)
- **DDI**
  - inhibits MAO – contra-indicated with MAO inhibitors
  - use with caution with e.g. SSRIs and tramadol
- **TDM?**

Isoniazide, INH

- Available as Nicotibine tablets, 300 mg and IV via import (Cemidon vials 300 mg/5 mL)
- **Dose**: 5 mg/kg, up to 300 mg per day, on empty stomach
- No dose adjustments
- **Main AEs:**
  - hepatotoxicity: use with caution in hepatic impairment
  - neurotoxicity, mainly peripheral, but use with caution in patients known with seizures
  - use with caution in patients with G6PD deficiency (risk for hemolysis)
  - pyridoxin deficiency
- Supplement pyridoxin (vitamin B6 – 25- 50 mg/day or 250 mg/week) should be provided
- **DDI:** potentiates hepatotoxicity of paracetamol, phenytoin, valproic acid and carbamazepine. Inhibits voriconazole metabolism.

Fluoroquinolones

- Moxifloxacin 400 mg/day, no dose adjustment
- Ciprofloxacin 500 – 750 mg, 2x/day, to be adjusted in renal insufficiency
- Longterm use might be associated with important AEs

80yr old patient on Steovit

34yr old pregnant woman

35 yr old, plays tennis very frequently

40 yr old woman, loves tanning

64 yr old man, treated with sotalol

40 yr old, with DMI

- Complexation with decreased absorption if taken with Ca, Mg, Fe, milk
- Teratogenic, not recommended in children
- Tendinopathy – tendon rupture
- Fototoxicity
- QTc prolongation
- Dysglycemia

Adverse event monitoring

- Recommended at initiation, and afterwards **each 1-2 months**
- Very common
- Importance of patient counseling – rapid recognition

Complete blood cell count	Linezolid >> rifampicin, rifabutin, cefoxitin, imipenem
Renal function (screat/ureum)	Dose adjustments for - Clarithromycin - Imipenem - Cefoxitin - Ciprofloxacin - Ethambutol - Rifabutin Cautious with amikacin
Liver function tests	Rifampicin, rifabutin, macrolides, clofazimine, INH, tigecycline
ECG - QTc interval	Macrolides, fluoroquinolones, clofazimine Especially when combined with comedication (Credible Meds List 1 – www.crediblemeds.org)
Audiogram, for hearing loss and tinnitus	Macrolides, amikacin
Visual acuity and color discrimination	Ethambutol, rifabutin (uveitis), linezolid (optic neuritis)
Clinical follow-up for neurotoxicity	INH (peripheral), ethambutol, linezolid (optic neuritis)
Clinical follow-up for tendinopathy	Moxifloxacine, ciprofloxacin

DDI management

- PK
  - Rifampicin & rifabutin are potent CYP450 inducers
  - Clarithromycin is a potent CYP450 inhibitor, azithromycin to a much lesser extent
  - Linezolid is a MAO-inhibitor
  - Ethambutol and FQ are complexed by divalent cations
- PD
  - Macrolides, FQ and clofazimine prolong the QTc interval
  - INH potentiates hepatotoxicity of paracetamol, phenytoin, valproic acid, carbamazepin

Check DDIs in an interactionchecker - https://reference.medscape.com/drug-interactionchecker (or call your clinical pharmacist)

Therapeutic drug monitoring?

- Standard practice for amikacine (and recommended but not available for streptomycin)

What about the other NTM agents?

- Clinical utility of performing TDM for the other NTM agents has not been addressed in RCTs
- Several observational studies documented
  - significant reduction in clarithromycin exposure due to rifampicin or rifabutin
  - decreased linezolid exposure due to rifampicin
- Besides, azithromycin exposure (Cmax) was found to be associated with outcome

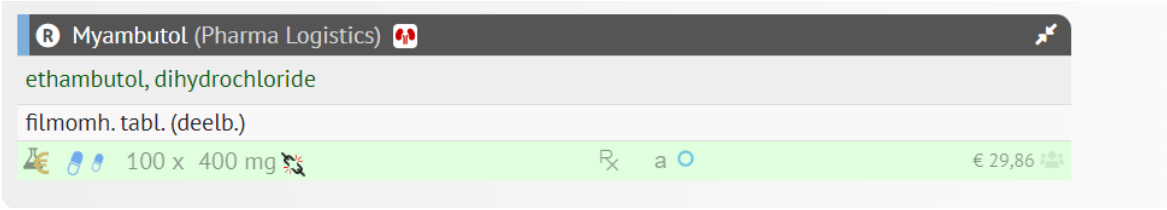
- NTM 2020 guideline recommends to consider TDM
  - in drug malabsorption
  - drug underdosing
  - in case of presumed DDIs
  - delayed sputum culture conversion

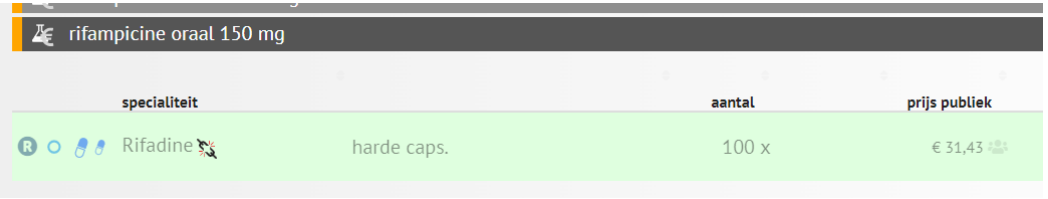
"Antituberculosis TDM panel" available at ULB (David Fage, Guillaume Deprez, Frederic Cotton) – INH, ethambutol, pyrazinamide, rifampicine/rifabutin, moxifloxacin, levofloxacine, linezolid, bedaquiline

Logistic & Reimbursement challenges

1. Frequent stock ruptures!

- Essential drugs for NTM treatment
- Shortages are not easy to manage
  - Often no alternatives
  - Limited stock only available in hospital pharmacies – impact on patient compliance





2. Many drugs have to be imported from other countries

- No Belgian reimbursement for imipenem, cefoxitin, clofazimine, …
- No reimbursement for tigecycline in OPAT
- High cost for the patient (only partially reimbursed by BSF)
- Initiative by BAPCOC-FAGG-RIZIV to explore reimbursement possibilities for NTM import drugs

Conclusion

- NTM 2020 guidelines recommend initiation of treatment rather than “watchfull waiting”
  - In patients with certain diagnosis, cavitary disease or at risk for progressive disease

- Taking the decision on initiating NTM treatment is difficult – also related to the different pharmacological challenges

  - Patients will be exposed to longterm treatment with a multidrug regimen
  - Tolerance might be difficult, adverse events are common
  - NTM treatment might often lead to drug-drug interactions

	Geneesmiddel	Merknaam	Import	Aankoop via	Prijs per stuk	Terugbetaling tijdens hospitalisatie	Terugbetaling ambulant	max dosing (mg)	max freq	Dagkost (totaal)
IV	Imipenem-cilastatine	IMIPENEM CILASTATINE-AUROBINDO FL INJ 20ML 500MG/500MG	ja	Ecopharmasupply	18,05	nee	nee	1000	3	108,3
	tigecycline	TYGACIL FL 50MG	nee	Pfizer	19,59	ja, ten laste forfait	nee	50	2	39,18
	amikacine	AMIKACINE FL INJ 100ML 10MG/ML	nee	Bbraun	10,24	ja, ten laste forfait	ja, cat B	15 mg/kg	1	10,24
	cefoxitine	CEFOXITIN VIAL 1G	ja	Added Pharma	16,25	nee	nee	4000	3	195
	cefoxitine	CEFOXITIN VIAL 2G	ja	Added Pharma	63,27	nee	nee	4000	3	379,62
	linezolid	ZYVOXID INFUUSZAK FREEFLEX 300ML 2MG/ML	nee	Pfizer	30,4	ja, ten laste forfait	ja, cat B	600	1	30,4
PO	clofazimine	LAMPRENE CAPS 100MG	ja	Ecopharmasupply	2,73	nee	nee	100	1	2,73
	clofazimine	LAMPRENE CAPS 50MG	ja	Ecopharmasupply	2,19	nee	nee			
	linezolid	ZYVOXID FILMTABLET 600MG	nee	Pfizer	28,48	ja, ten laste forfait	ja, cat B	600	1	28,48
	azithromycine	ZITROMAX TABL 500MG	nee	Pfizer	1,23	ja, ten laste forfait	ja, cat C	500	1	1,23
	azithromycine	ZITROMAX TABL 250MG	nee	Pfizer	0,61	ja, ten laste forfait	ja, cat C	250	1	
	ethambutol	MYAMBUTOL TABL 400MG	nee	Teofarma via PL	0,21	ja	ja, cat A	15 mg/kg	1	0,84
	doxycycline	VIBRATAB TABL 100MG	nee	Pfizer	0,17	ja, ten laste forfait	ja, cat C	100	2	0,34
	moxifloxacine	AVELOX 400 TABL 400MG	nee	Bayer	1,37	ja, ten laste forfait	ja, cat C	400	1	1,37
	rifampicin	RIFADINE CAPS 300MG	nee	Sanofi	0,46	ja, ten laste forfait	ja, cat C	600	1	0,92
	rifabutin	MYCOBUTIN CAPS 150MG	nee	Pfizer	2,13	ja, ten laste forfait	ja, cat A	300	1	4,26
	isoniazid	NICOTIBINE TABL 300MG	nee	Econophar	0,37	ja, ten laste forfait	ja, cat A	300	1	0,37

Management of hepatotoxicity

- Withhold treatment
  - if AST/ALT or GGT/AP are > 5 times ULN
  - or when > 3 times ULN with symptoms
- If treatment cannot be interrupted: change to a less hepatotoxic regimen, e.g. FQ, EMB, parenteral amikacin – depending on the type of NTM
- After AST/ALT or GGT/AP returns to < 2 times ULN, restart drugs one by one every 3-7 days

Bergeron A et al. Lancet Infect Dis. 2022, Accepted for publication.

Antituberculosis panel - slide courtesy D. Fage

	Drugs	Abbreviations	Daily dose	Therapeutic targets C_{2h} (mg/L)
First-line	Isoniazid	INH	5 mg/kg	3 – 6
	Ethambutol	EMB	20 mg/kg	2 – 6
	Pyrazinamide	PZA	25 mg/kg	20 – 60
	Rifampicin	RMP	10 mg/kg	8 – 24
Second-line	Rifabutin	RFB	5 mg/kg	C_{3h}: 0.45 – 0.90
	Moxifloxacin	MFX	400 mg/day	3 – 5
	Levofloxacin	LFX	500 -1000 mg/day	8 – 13
	Linezolid	LZD	600 mg/day	12 – 26
	Bedaquiline	BDQ	**LOD**: 400 mg/d during 2 weeks **Continuation**: 200 mg 3x/week	C_0: >0.6

Asultan *et al*., Drugs (2014) 74:839–854
Nahid *et al.,* Clin. Infect. Dis. (2016) 63(7): e147–e195
Perrineau *et al.,* Medecine et maladie infectieuse (2016) 46: 79-84