Infections by nontuberculous mycobacteria

Clinical cases

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Case 1
Ms. P.
The usual starting point

- Your colleague from the molecular diagnostic lab calls
- ‘It’s *Mycobacterium chimaera*!’
The patient

• Ms. P., 60 years old

• History: COPD, GOLD stage II
• 2012 Oesophageal carcinoma w/ resection (esophagectomy)
• 2015 Breast cancer, surgical treatment and radiotherapy

• 4 months of productive cough, malaise, fatigue

• C-reactive protein: 16
• IgG antibodies to Aspergillus >200 mg/l
• IgE antibodies to Aspergillus <0.35
Diagnostic work-up

- Auramine stain of sputum: 2+
- MGIT Time to Positivity 7 days 21 hours
- 4/4 cultures positive over 2 months

Susceptibility testing?  
Treat?
Diagnosis of NTM pulmonary disease

American Thoracic Society diagnostic criteria*

- **Symptoms** compatible with NTM lung disease
- **Radiology** compatible with NTM lung disease (cavities / nod.-bronch.)
- Obtain ≥3 respiratory samples, over the course of at least a week
- Disease: At least **2 positive cultures** with the same species

*Lab:*
- always use solid + liquid media
- Identify all isolates by molecular methods => *nomen est omen*

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*Griffith DE, et al., Am J Respir Crit Care Med 2007; update in progress
Treatment recommendations

American Thoracic Society / Infectious Diseases Society of America

- *M. avium* complex  rifampicin-ethambutol-azithromycin (or clarithro)
  - + 3mo streptomycin / amikacin if very severe

- With **surgical debulking** whenever feasible

Treatment duration
- Pulmonary disease: 12 months after culture conversion

Regimen selection — Regimen selection depends, in part, on susceptibility to macrolides; most MAC isolates, particularly in patients who have not been treated before, are macrolide susceptible. For most treatment of patients with MAC lung disease, we generally choose a three-drug regimen containing a macrolide, a rifamycin, and ethambutol. For patients who have severe or fibrocutaneous disease, a parenteral aminoglycoside is also often used in the initial phase of treatment.

Our preferred macrolide and rifamycin are azithromycin and rifampin, respectively. The dosing depends on the type and severity of disease and patient weight. (See Mild to moderate nodular bronchiectatic disease, below, and Fibrocutaneous or severe disease, below.)

The following regimen recommendations are consistent with the 2007 guidelines on nontuberculous mycobacteria from the American Thoracic Society and Infectious Diseases Society of America [15]. These guidelines apply to patients with cystic fibrosis as well.

Macrolide-susceptible infection — The vast majority of patients without prior treatment for MAC have macrolide-susceptible infection.

Mild to moderate nodular bronchiectatic disease — For most patients with mild to moderate nodular bronchiectatic disease, we suggest a three-times weekly regimen of:

- **Azithromycin** (500 mg three times per week) PLUS
- **Rifampin** (600 mg three times per week) PLUS
- **Ethambutol** (15 mg/kg three times per week)

If cost or availability is an issue, clarithromycin (1000 mg three times per week) can be substituted for azithromycin. If the patient is taking drugs that interact with rifampin or the patient has hepatotoxicity to rifampin, rifabutin (300 mg three times per week) can be substituted.

Fibrocutaneous or severe disease — For most patients with fibrocutaneous MAC lung disease or severe nodular bronchiectatic disease, we suggest a daily regimen of:

- **Azithromycin** (250 to 600 mg daily) PLUS
- **Rifampin** (600 mg daily) PLUS
- **Ethambutol** (15 mg/kg daily)

In addition, we suggest using parenteral streptomycin or amikacin (both 10 to 15 mg/kg three times per week) as a fourth agent for the first 8 to
Case 2
Mr. G.
The patient discussed at grand round

- Mr. G., 73 years old
- History: type II diabetes, asthma, hypertension, NSTEMI (2013)
- No history of smoking, worked in aluminium production and a shipyard

- Since one year: increase in asthma exacerbation frequency
- Recent cultures: *P. aeruginosa* (2016), *S. maltophilia*, *S. marcescens*
- **2x Mycobacterium abscessus** over 6 months

- Dyspnea (slight), productive cough, fatigue

- C-reactive protein: 11
- ESR: 12 mm/hr
- IgG antibodies to Aspergillus 23 mg/l (ref 0-39)
- IgE antibodies to Aspergillus 224 mg/l (ref <100)
Further work-up

- 7 cultures, 4 positive for *M. abscessus* (1 BAL)
- All sputum samples auramine stain negative

- Susceptibility testing:
  - Cefoxitin & imipenem
  - Amikacin
  - Clarithromycin
  - Linezolid
  - Tigecycline
  - Clofazimine
- Everything else: R!

- ECG: QTc interval 500ms (pre-existing)
Treatment recommendations

American Thoracic Society / Infectious Diseases Society of America

- *M. abscessus*
  - Phase 1: amikacin, imipenem, tigecycline, clofazimine, azithromycin
  - Phase 2: azithromycin, minocycline?, ciprofloxacin?, clofazimine?, inhaled amikacin?

- With surgical debulking whenever feasible

Treatment duration
- Pulmonary disease: 12 months after culture conversion

NTM essentials
4 distinct NTM disease entities

- NTM pulmonary disease (90% of the NTM disease case load)
- NTM cervicofacial lymphadenitis in immunocompetent children
- Disseminated NTM disease in the severely immunocompromised
- Skin/soft tissue infection or osteomyelitis after inoculation
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Clinical relevance of pulmonary NTM isolates in NL

Clinical relevance differs by species!
(% of patients who met diagnostic criteria, per species)

van Ingen J et al., Thorax 2009
van Ingen J et al., Infect Gen Evol 2011
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- *M. abscessus* amikacin, imipenem, tigecycline, clofazimine, azithromycin

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Natural resistance

- Cell wall impermeability
  Rifamycins, β-lactams, quinolones

- Efflux pumps
  Tetracyclins, quinolones

- Biotransformation
  Aminoglycosides, β-lactams, quinolones

- WhiB7 ‘resistome’: inducible
  Macrolides (erm), rifamycins (rbpA)

The myth:

“There is poor correlation between \textit{in vitro} and \textit{in vivo} drug activity in NTM”

Source: numerous reviews and textbooks
Typically written by TB specialists
**In vitro – in vivo correlations**

*Mycobacterium avium* complex pulmonary disease

- BTS trial rifampicin-ethambutol: 27% ‘cure rate’
- Rifampicin / ethambutol MICs 20-40 times higher than for *M. tuberculosis*
  - And above PK/PD targets, even if tested in combination
- Poorly active => poor outcomes => PERFECT in vitro-in vivo correlation
  
- RIF-EMB-macrolide regimen
- Clarithromycin susceptible: 75% prolonged culture conversion
- Clarithromycin resistant: 25% prolonged culture conversion

- **Clear role for macrolide susceptibility testing**

- Recent data: amikacin MICs >64 mg/l associated with 16S mutations
  - And prolonged aminoglycoside exposure and treatment failure


In vitro – in vivo correlations (2)

- *M. abscessus* pulmonary disease
  - Macrolide, amikacin, cefoxitin/imipenem, tigecycline, linezolid
    - Based (init
    - 69pt, 48%
  - 4wk cefoxitin-amikacin, then ciprofloxacin-doxycycline-clarithromycin
    - Regardless
    - 65pt, 58%
    - But: 30% in macrolide inducible R strains, 80% in macrolide susceptible!

- *M. abscessus* extrapulmonary disease
  - 47 pt, 72% cure w/amikacin-cefoxitin, based on AST

- Drugs to test: cefoxitin, amikacin, clarithromycin (inducible resistance!)

Which method?

- Only broth microdilution was tested in trials
  - Cation-adjusted Mueller Hinton medium

- NO E-tests => lack of reproducibility
- NO Proportion methods => no breakpoints
- NO MGIT (yet) => no breakpoints
Take home messages

- Sterile sites: NTM isolation = disease (unless...)

- Pulmonary specimens: apply ATS/IDSA diagnostic criteria
  - And ‘nomen est omen’ if you know your local situation
  - Not all NTM are created equal...

- Treatment = multi-drug, long, toxic and many interactions
  - MAC: RIF-EMB-macrolide (60-70% cure rate)
  - M. kansasii: INH-RIF-EMB or RIF-EMB-macrolide (95% cure rate)
  - M. abscessus: IMI/FOX-AMI-macrolide (clofa? Tige?) (50% cure rate)
  - Don’t try this at home... seek expert referral

- Susceptibility testing is helpful, if done right and reported right
- Essential: macrolides (+inducible R), amikacin
Thanks for your attention! Have a great Summer School!

And remember: NTM-911 = Jakko.vanIngen@radboudumc.nl // M +31-6-30825431