NTM case studies

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Conflicts of interest

• I have shares in and consult for Savara pharmaceuticals which has active research in GM-CSF for NTM infection
Case 1

• 63 y.o lady
• Productive cough – small volumes
• Weight loss ~10kg over 12 months (BMI now 18)
• General malaise
• Only other problem hypertension
More details..

Sputum x 3 M. avium

Normal Hb, WCC, liver function, renal function

On diltiazem for her hypertension
Would you ...

• A. Wait for 6 months and repeat the imaging
• B. Start clarithromycin/rifampicin/ethambutol
• C. Start azithromycin/rifampicin/ethambutol
• D. Start something else
Criteria for treatment

- Consistent radiology
- At least 2x culture of same NTM from sputum or 1x from invasive sample (biopsy)
- Symptoms - weight loss, cough
- Ready and willing for the ride ...
  - Cure rate on intention to treat about 50%
  - Recurrence rate at 3 years post “cure” 50%+
<table>
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<tr>
<th>M. avium complex-pulmonary disease</th>
<th>Antibiotic regimen</th>
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<td><strong>Non-severe MAC-pulmonary disease</strong> (ie, AFB smear-negative respiratory tract samples, no radiological evidence of lung cavitation or severe infection, mild-moderate symptoms, no signs of systemic illness)</td>
<td>Rifampicin 600 mg 3× per week and Ethambutol 25 mg/kg 3× per week and Azithromycin 500 mg 3× per week or clarithromycin 1 g in two divided doses 3× per week Antibiotic treatment should continue for a minimum of 12 months after culture conversion.</td>
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Macrolide problems

- Clarithromycin inhibits cytochrome P450
- Diltiazem is partly metabolised by P450
- Azithromycin does not inhibit P450
- All macrolides can prolong the QT interval
- Regimes without macrolides have a much lower success rate
This lady

- Azithromycin 500mg 3x/week, rifampicin 450mg daily, ethambutol 15mg/kg
- Staggered start taking 1 month to full dosing
- Week 4 AST doubled to 84 (normal 45)
- Week 5 AST 93
- Week 6 AST 310, nausea ++++, RUQ pain
- Rifampicin stopped
- Clofazimine started when AST dropped to 50
- Last positive culture at 8 months
- Therapy stopped at 20 months
- Culture positive again 2 years post treatment
Treatment duration?

- **ATS guidelines**
  - 1 year after the last +ve sputum culture

- **BTS guidelines**
  - 2 years and at least 12/12 past last positive sputum culture
  - kansasii 9 months + 12 months clear
  - cheloneae, szulgai indefinite
Case 2

- 58 y.o man
- Itinerant, no fixed abode
- Presented with “feeling unwell”
- Smoked cigarettes and drank alcohol “as often as I can get them”
More details ..

Sputum x 3 M. abscessus
Hb 90, iron deficient
Mildly abnormal LFT’s (AST 45, ALT 65)
Liver ultrasound “focal cirrhosis”
Normal renal function
Would you …

• A. Wait for 6 months and repeat the imaging
• B. Start clarithromycin/rifampicin/ethambutol
• C. Start iv meropenem/amikacin/tigecycline
• D. Do something else
*M. abscessus* is a different disease

- Highly resistant
- Often rapidly progressive
- The one NTM you should definitely consider surgery if feasible
### Table 8  
Suggested antibiotic regimens for adults with *Mycobacterium abscessus-*pulmonary disease

<table>
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<th>M. abscessus</th>
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| Clarithromycin sensitive or inducible macrolide-resistant isolates | **Initial phase:** ≥1 month†  
intravenous amikacin 15 mg/kg daily or 3× per week‡ and  
intravenous tigecycline 50 mg twice daily and where tolerated  
intravenous imipenem 1 g twice daily and where tolerated  
oral clarithromycin 500 mg twice daily or oral azithromycin 250–500 mg daily  
**Continuation phase:**  
nebulised amikacin†  
and  
oral clarithromycin 500 mg twice daily or azithromycin 250–500 mg daily  
and 1–3 of the following antibiotics guided by drug susceptibility results and patient tolerance:  
oral clofazimine 50–100 mg daily§  
oral linezolid 600 mg daily or twice daily  
oral minocycline 100 mg twice daily  
oral moxifloxacin 400 mg daily  
oral co-trimoxazole 960 mg twice daily | **Initial phase:** ≥1 month†  
intravenous amikacin 15 mg/kg daily or 3× per week‡ and  
intravenous tigecycline 50 mg twice daily and where tolerated  
intravenous imipenem 1 g twice daily  
**Continuation phase:**  
nebulised amikacin†  
and  
2–4 of the following antibiotics guided by drug susceptibility results and patient tolerance:  
oral clofazimine 50–100 mg daily§  
oral linezolid 600 mg daily or twice daily  
oral minocycline 100 mg twice daily  
oral moxifloxacin 400 mg daily  
oral co-trimoxazole 960 mg twice daily |

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BTS guidelines  
Haworth et al Thorax 2017
This man

- Iv Amikacin/Cefoxitin/Meropenem for 6 weeks
- Switch to nebulised amikacin, oral clofazimine + moxifloxacin + co-trimoxazole
- Died on therapy of presumed AMI at 32 weeks of therapy, still culture positive at 26 weeks
What is coming in NTM?

• Inhaled antibiotics “up front”
  – Amikacin (liposomal) Inzmed
  – Other potential inhaled antibiotics (e.g. ciprofloxacin)

• Newer TB drugs
  – Bedaquiline shows promise – cross resistance with clofazimine

• Immune stimulants
  – Interferon gamma failed in phase III
  – Systemic IL-12 never reported presumed negative
  – GM-CSF phase II Savara

• Other!
  – Inhaled NO
  – Biofilm inhibitors
Thank you!

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