NTM case studies

Grant Waterer
MBBS PhD MBA FRACP FCCP MRCP
Professor of Medicine, University of Western Australia
Professor of Medicine, Northwestern University, Chicago

Register now at congress.chestnet.org
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>
<thead>
<tr>
<th>M. avium complex-pulmonary disease</th>
<th><strong>Antibiotic regimen</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-severe MAC-pulmonary disease</strong></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</td>
</tr>
<tr>
<td>(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>Antibiotic treatment should continue for a minimum of 12 months after culture conversion.</td>
</tr>
<tr>
<td><strong>Severe MAC-pulmonary disease</strong></td>
<td>Rifampicin 600 mg daily and Ethambutol 15 mg/kg daily and Azithromycin 250 mg daily or clarithromycin 500 mg twice daily and consider intravenous amikacin for up to 3 months or nebulised amikacin</td>
</tr>
<tr>
<td>(ie, AFB smear-positive respiratory tract samples, radiological evidence of lung cavitation/severe infection, or severe symptoms/signs of systemic illness)</td>
<td>Antibiotic treatment should continue for a minimum of 12 months after culture conversion.</td>
</tr>
<tr>
<td>M. xenopi-pulmonary disease</td>
<td>Antibiotic regimen</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td><strong>Non-severe M. xenopi-pulmonary disease</strong> (i.e., 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 daily and Ethambutol 15 mg/kg daily and Azithromycin 250 mg daily or clarithromycin 500 mg twice daily and Moxifloxacin 400 mg daily or isoniazid 300 mg (+pyridoxine 10 mg) daily Antibiotic treatment should continue for a minimum of 12 months after culture conversion.</td>
</tr>
<tr>
<td><strong>Severe M. xenopi-pulmonary disease</strong> (i.e., AFB smear-positive respiratory tract samples, radiological evidence of lung cavitation/severe infection, or severe symptoms/signs of systemic illness)</td>
<td>Rifampicin 600 mg daily and Ethambutol 15 mg/kg daily and Azithromycin 250 mg daily or clarithromycin 500 mg twice daily and Moxifloxacin 400 mg daily or isoniazid 300 mg (+pyridoxine 10 mg) daily and consider intravenous amikacin for up to 3 months or nebulised amikacin Antibiotic treatment should continue for a minimum of 12 months after culture conversion.</td>
</tr>
</tbody>
</table>
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
  – chelonae, 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>
<thead>
<tr>
<th><em>M. abscessus</em></th>
<th>Antibiotic regimen</th>
<th>Constitutive macrolide-resistant isolates</th>
</tr>
</thead>
</table>
| Clarithromycin sensitive isolates 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 |

---

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!

- grant.waterer@uwa.edu.au