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NTM case studies



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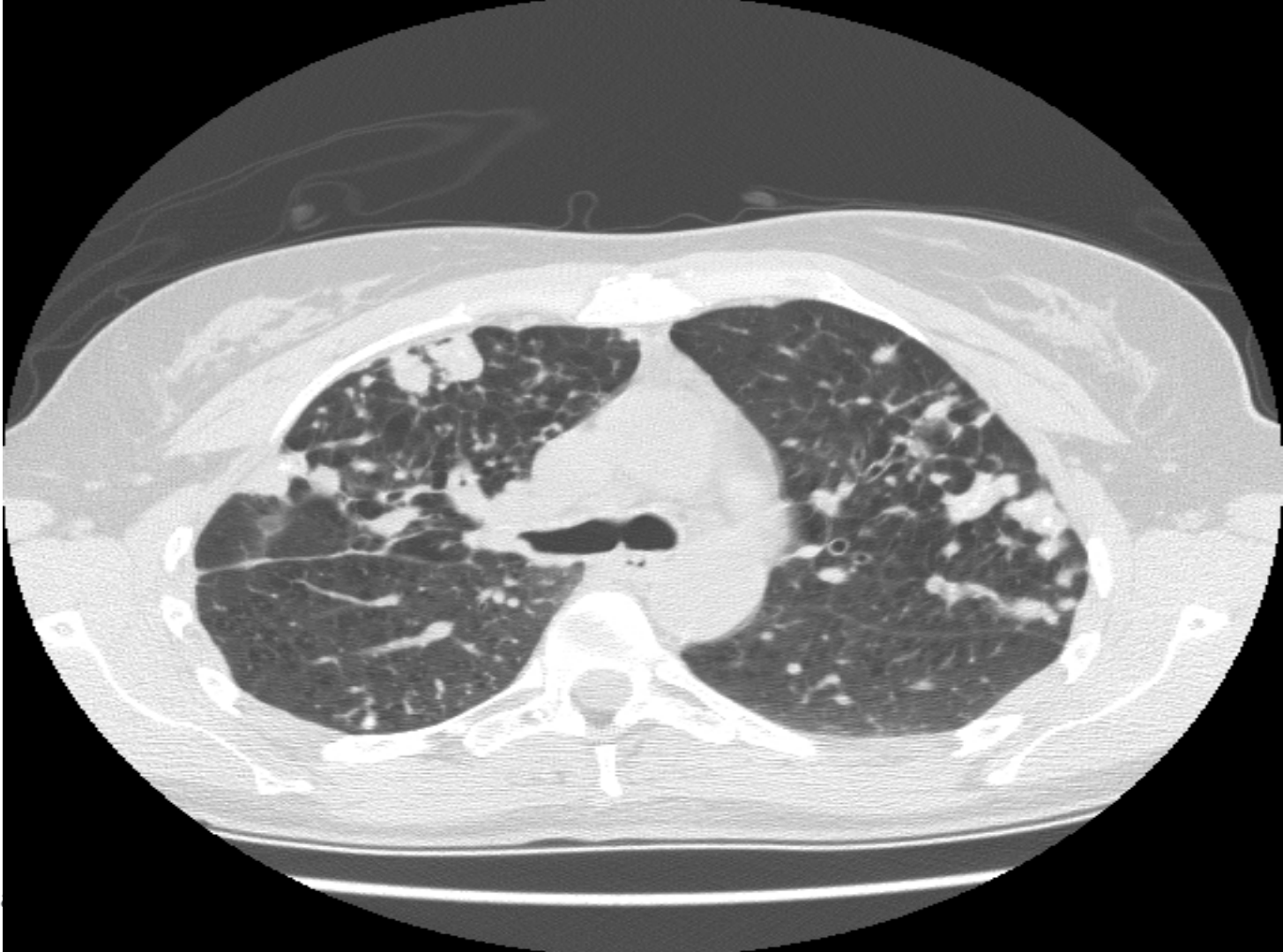
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Conflicts of interest

- 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



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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%+

<i>M. avium</i> complex-pulmonary disease	Antibiotic regimen
Non-severe MAC-pulmonary disease (ie, AFB smear-negative respiratory tract samples, no radiological evidence of lung cavitation or severe infection, mild-moderate symptoms, no signs of systemic illness)	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.
Severe MAC-pulmonary disease (ie, AFB smear-positive respiratory tract samples, radiological evidence of lung cavitation/severe infection, or severe symptoms/signs of systemic illness)	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 Antibiotic treatment should continue for a minimum of 12 months after culture conversion.

BTS guidelines
Haworth et al Thorax 2017

Table 6 Suggested antibiotic regimens for adults with *Mycobacterium xenopi*-pulmonary disease

<i>M. xenopi</i> -pulmonary disease	Antibiotic regimen
Non-severe <i>M. xenopi</i>-pulmonary disease (ie, AFB smear-negative respiratory tract samples, no radiological evidence of lung cavitation or severe infection, mild-moderate symptoms, no signs of systemic illness)	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.
Severe <i>M. xenopi</i>-pulmonary disease (ie, AFB smear-positive respiratory tract samples, radiological evidence of lung cavitation/severe infection, or severe symptoms/signs of systemic illness)	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.

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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
 - 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”



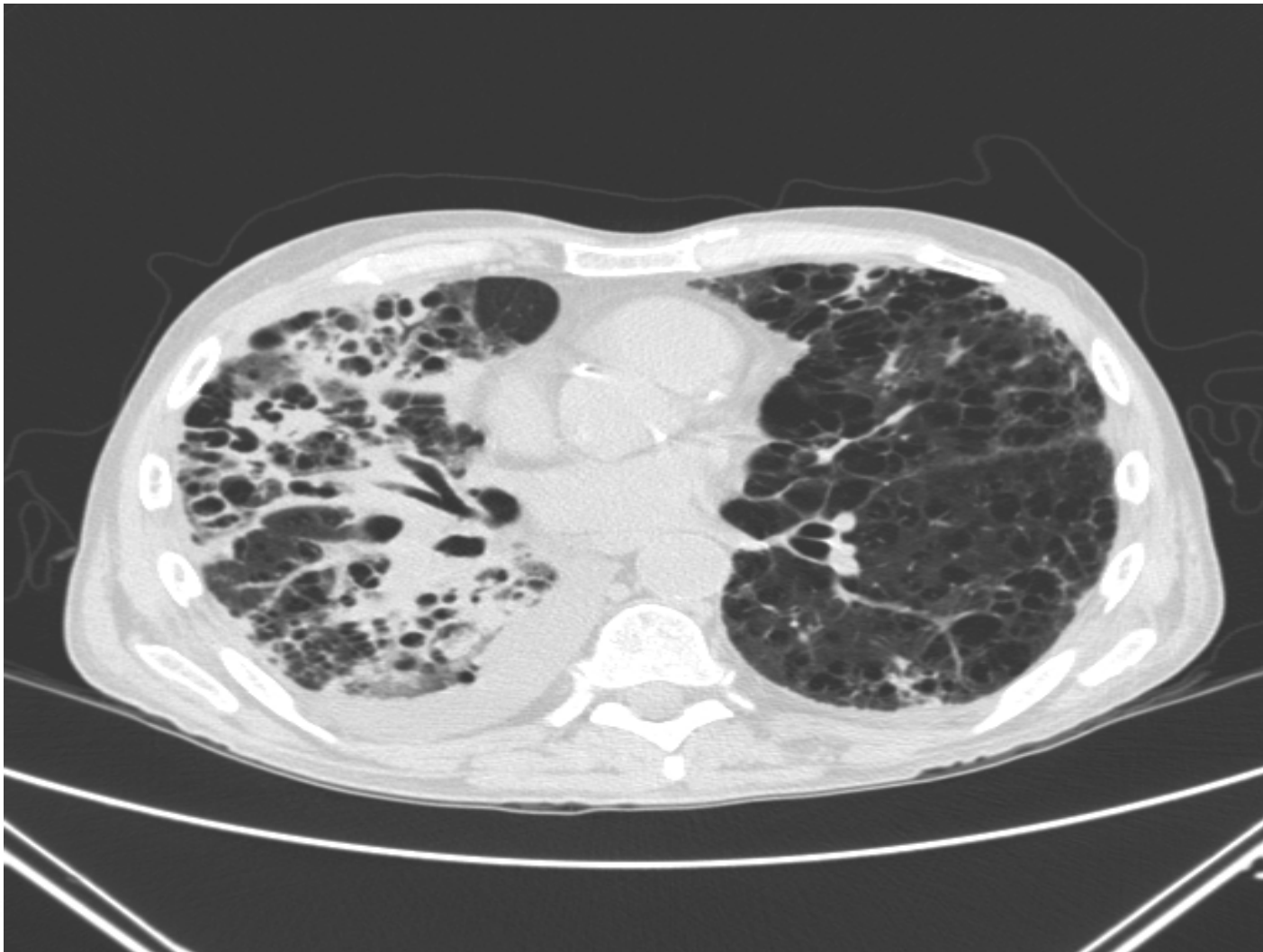
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More details ..

Sputum x 3 M.abcessus

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

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

Constitutive 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

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!

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