

Kill 'em all!

The quest for an antibiotic regimen that cures non-tuberculous mycobacterial disease

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DISCLOSURES

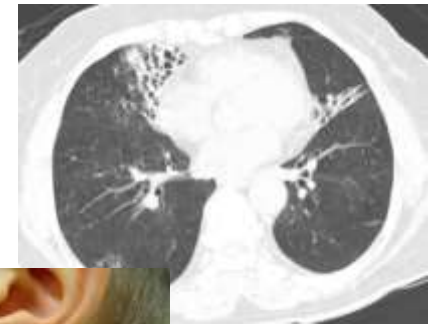
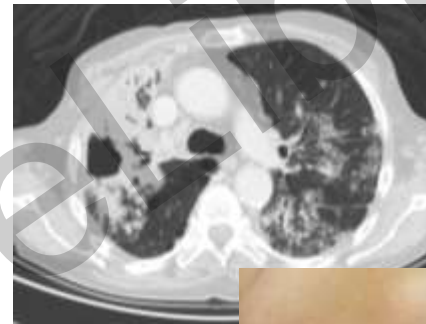
Nature	Source
Advisory board membership	Insmed, Inc. (ALIS – liposomal amikacin)
	Spero Therapeutics
	Janssen Pharmaceuticals (bedaquiline)
Participation in clinical trials (lab)	Insmed, Inc.
Investigator initiated research grants	Pfizer (tigecycline)
	Neem Biotech

NTM – what's that?



What does NTM disease look like?

- **Chronic pulmonary infections**
 - Fibro-cavitary
 - Nodular-bronchiectatic
- Lymphadenitis in children
- Skin infections after inoculation
- Disseminated disease

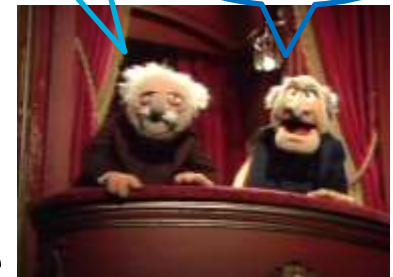


So... what's the problem?

- NTM are **intrinsically resistant** to most classes of antibiotics
- *M. avium* regimen: rifampicin, ethambutol, azithromycin (+/- amikacin)
- *M. abscessus* regimen: imipenem, amikacin, tigecycline, azithromycin, ...?
- Treatment **duration**: 1.5 – 2 years
- Cure rates: 40% (*M. abscessus*) – 70% (*M. avium* complex)
- **Recurrence** rate: 40%
- Regimens largely based on case series, not on **PK/PD** science

Horrendous!

SO bad!



The regimen development track

MIC

- Minimum inhibitory concentration / minimum bactericidal concentration
- **How active is this drug?**

SYN

- Checkerboard titrations / Fractional inhibitory concentration index
- **Is this drug synergistic with other antimycobacterial drugs?**

TKK

- Time-Kill kinetics assay
- **Is killing time/concentration/exposure dependent?**

MCF

- Antimycobacterial activity inside macrophages
- **Is this drug/regimen effective against intracellular mycobacteria?**

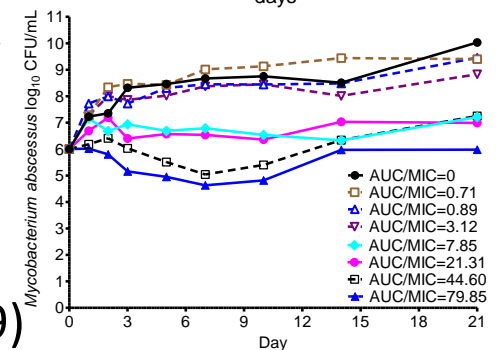
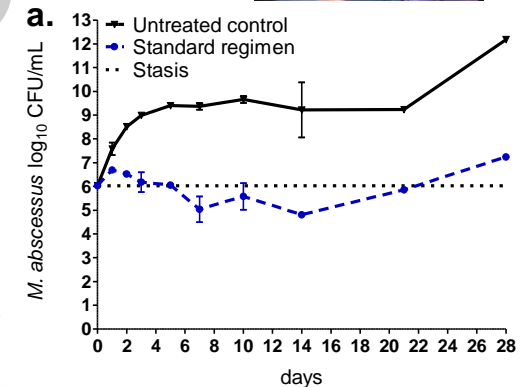
HFS

- Hollow fiber pharmacodynamic model
- **What is the optimal dose, dosing strategy and treatment duration?**

Can we beat *M. abscessus*?

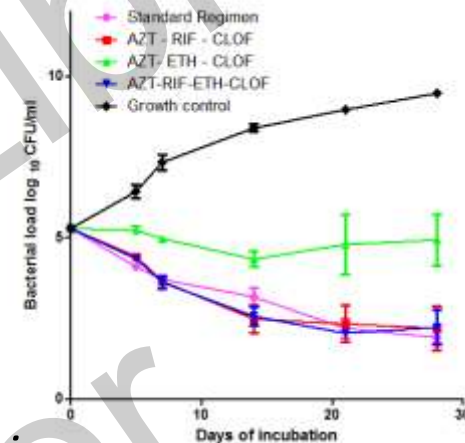


- Hollow fiber model, work by Beatriz Ferro, PhD
 - Current regimen only maintains **stasis**
 - Moxifloxacin has no effect at all
- **Tigecycline** is active, but at intolerable doses
- Potential new leads:
 - **Tedizolid** (Mike Ruth, Monday 13:30 **P#2122**)
 - TrxR inhibitors (Mike Ruth, Monday 13:30 **P#2120**)
 - Clofazimine-bedaquiline (Mike Ruth et al., JAC 2019)
- Multiple new molecules in early phases of development

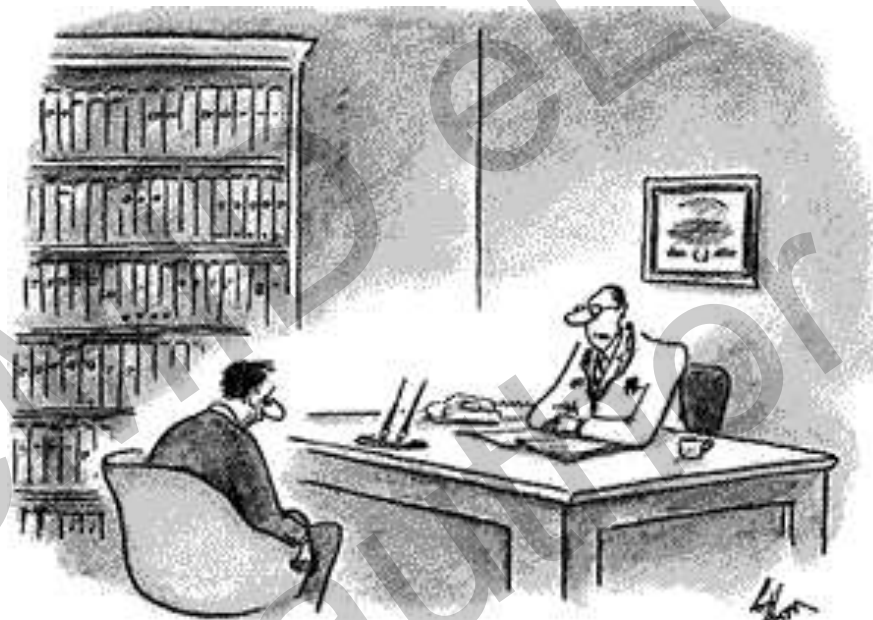


Hit the road, MAC...

- *M. avium* standard regimen does **not sterilize**
- **Clofazimine** can replace ethambutol
 - But perhaps not the rifamycin
 - Mike Ruth, Monday 13:30 P#2119
- **Minocycline** 200mg od is potent against *M. avium*
 - Mike Ruth et al., JAC, In press
- **Pentamidine** inhalation may work!
 - Mike Ruth, Monday 13:30 P#2121
- Up next: **clofazimine-bedaquiline**
 - Mike Ruth et al. JAC 2019



The race for a cure has started!



"Unfortunately, there's no cure—there's not even a race for a cure."

Thanks to my friends and mentors

Medical Microbiology



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Infectious Diseases



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Mycobacteriology team



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