Atypical Mycobacteria
= NTM (non TB Mycobacteria)
= MOTT (Mycobacteria other than TB)
المتفطرات اللانموذجية

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Mycobacteria

- **TB complex**: - MTB (hominis)
  - bovis
  - bovis BCG
  - africanum
- **NTM** (non-TB Mycobacteria)
  = **MOTT** (Mycobacteria other than TB)
  = **atypical** Mycobacteria
- **M. Leprae**: - paucibacillary (tuberculoid)
  - multibacillary (lepromatous)
- **M. ulcerans**: - mostly in Africa (rural wetlands)
  - skin lesions (painless nodule → large ulcer), may disseminate to distant skin or bone
  - treated by surgery (wide excision)

MOTT = NTM

Major clinical syndromes

- Pulmonary: MAC (MAI): Avium / Intracellare
  Kansasii
  Abscessus
  rarely: Fortuitum / Xenopi / Genavense /
  Gordonae (mostly contaminant)
- Cutaneous: Haemophilum
  Marinum
  rapid-grower: Fortuitum / Chelonae / Abscessus
- Lymphatic (lymphadenitis): MAC (MAI)
  Scrofulaceum
- disseminated: MAC (MAI)
  Hemophilum

MOTT = NTM

Cervical lymphadenitis:

adults:	90%	MTB		
children:	90%	NTM	3/4	MAC
			1/4	Scrofula

MOTT = NTM

- Environmental organisms (soil, water)
  even in tap water (M. Kansasii)
- **No** human to human transmission
- Colonization vs real infection
- Real infection: ATS guidelines:
  clinical symptoms
  + cavities/ nodules (Cxray or CT)
  or multifocal bronchiectasis (HRCT)
  + positive AFB cultures
  sputum x 2 or BAL or Bx
- PCR is available for: MTB
  NTM (MAC, Kansasii, Marinum, Gordonae)

multiplex PCR being developed for all NTM

MOTT = NTM

MAC (MAI)

can cause:

- pulmonary disease with underlying **lung** disease
- pulmonary disease in females non-smoker (**Lady Windermere's syn**)
- pulmonary disease in children with **cystic fibrosis**
- **cervical** lymphadenitis in children
- **hot tub lung** = HTL (allergic reaction)
- pulmonary **nodules** (like CA)
- **disseminated** disease in AIDS patients (CD4 < 50)

→ prophylaxis with clarithromycin 500 mg bid

or azithromycin 1200 mg qw

MAC (MAI)

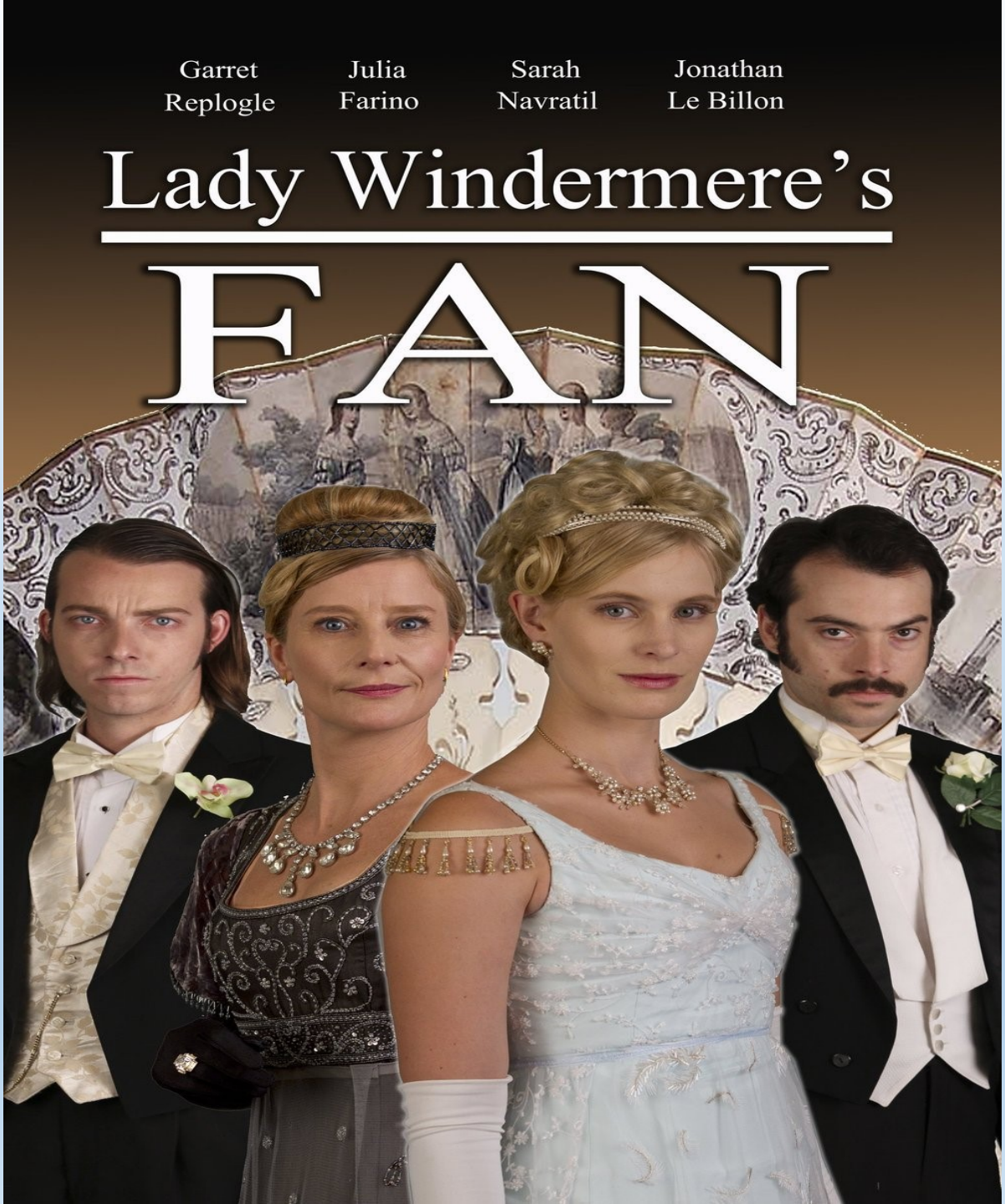
- **MAC Pulmonary disease:**
  - underlying structural lung disease (COPD, bronchiectasis, pneumoconiosis, old TB)
  - clinically like TB with chronic progressive course, and tendency to cavitate
  - often AFB smear positive
  - treated by anti-MAC, and may require surgery to cure

MAC (MAI)

- **MAC in cystic fibrosis (CF):**
  - **4-20%** of cystic fibrosis patients colonized with NTM (MOTT)
  - **80%** MAC & **20%** M. abscessus
  - difficult to distinguish colonization from real disease (**20%** meets ATS guidelines for pulmonary disease)
  - culture for NTM is recommended **yearly** for CF patients
  - treatment is indicated is ATS criteria is met

MAC (MAI)

- **Lady Windermere's syndrome:**
  - **nodular bronchiectasis** in older women without preexisting lung disease
  - may need HRCT to diagnose
  - slowly progressive disease (cough, wt loss)
  - usually associated with **MAC,** less by M. abscessus
  - from Oscar Wilde play (Lady Windermere's Fan), about a fastidious female character who **never cough**
  - affect **RML** & **L lingula**, more dependent on voluntary expectoration
  - treated by **anti-MAC**, sometimes by surgery to resect the infected lung regions


Garret Replogle
Julia Farino
Sarah Navratil
Jonathan Le Billon
Lady Windermere's
FAN

MAC (MAI)

- **Hot tub lung (HTL):**
  - diffuse **granulomatous** lung disease
  - inhalation of hot water **aerosol** containing NTM (mostly MAC)
  - **not** an infection, but a body reaction to the bacteria (**hypersensitivity** pneumonitis)
  - contaminated **water** in whirlpools, swimming pools, spas, saunas, showers & humidifiers
  - treated by **removal** of exposure, sometimes by **steroids**, rarely by anti-MAC

NTM = MOTT

M. Kansassi

- found in tap **water** in some cities
- pulmonary syndrome similar to TB with **upper** lobe disease and **cavities**
- pulmonary & disseminated disease in AIDS patients with CD4 < 200
- treatment is indicated in most cases

NTM = MOTT

M. Haemophilum

- needs **hemin** in media to grow
- needs incubation at **cooler** temp to grow
  (**30-32 °C** , rather than 37 °C)
- painful **nodular** lesions on extremities, may involve bone
- **disseminated** disease in AIDS disease

NTM = MOTT

M. Marinum

- grows optimally at **30-32°C**
- chronic cutaneous **ulcer,** with **sporotrichoid** involvement of limb
- exposure to fresh & salt water:
  often **fish tank**, or being cut by shelfish or **fins**
- treatment is indicated, with excellent prognosis


A
B

NTM = MOTT

Rapid Growers

- **Fortuitum**, **Chelonae**, **Abscessus**, others
- all species cause **skin** disease
- may grow in **1-3 d** in liquid media
- indolent **skin** infection after plastic surgery, liposuction, tattoos, acupuncture …
- indolent **pulmonary** disease (Abscessus > Fortuitum)
- treatment is indicated, with excellent prognosis

Anti-TB Therapy

- **Initial** phase: **<u>2 mon</u>** :

  4 drug regimen: if INH or rifa resistance > 4% :

  Rifa (RMP) + INH + PZA + EMB (or Strep)

  3 drug regimen: if INH or rifa resistance < 4% :

  Rifa (RMP) + INH + EMB (or Strep)

  rifampin = rifampicin (Rifadin, Rimactane) 300 mg 2 tab qd

  isoniazid (Nydrazid) 300 mg 1 tab qd → with B6 25-50 mg qd

  PZA 25-35 mg /kg/d (500 mg 2-4 tab qd) → max 3 g

  [**not** in preg & **not** for bovis/bovis BCG/ Kansasii]

  Ethambutol (Myambutol) 15-25 mg/Kg/d (400 mg 2-4 tab qd)

  → max 2.5 g

- **Continuation** phase: **<u>4-7 mon</u>** : [? for TB meningitis: 12-18 mon]

  2 drug regimen: **Rifa + INH**

  7 mon for: all HIV (expert opinion)

  cavitary lesions

  + sputum culture at 2 mon (end of initial phase)

  cannot tolerate PZA

Anti-TB Therapy

- **Rifamycin** derivatives:

  absorbable: for TB:

  - rifampin (Rifadin, Rimactane) 300 mg 2 tab qd
  - rifabutin (mycobutin) 150 mg 2 tab qd

    → preferred with most HAART (cART)
  - rifapentine (Priftin) 150 mg 4 tab biw (initial phase)

    150 mg 4 tab qw (continuation phase)

    150 mg 6 tab qw x 12 w (LTBI : with INH)

    150 mg 8 tab qd (new shorter regimen)

  non-absorbable: for other uses:

  - rifaximin (Xifaxan, Normix) 200 mg tid x 3 d (traveler's diarrhea)

    550 mg bid (hepatic encephalopathy)

    550 mg tid x 2 w (IBS-D)

    400 mg tid x 20 d after 10 d of PO vanco

    (CDI) → off label
  - rifamycin (Aemcolo): 194 mg 2 tab bid x 3 d (traveler's diarrhea)

Anti-TB Therapy

- **2nd line** anti-TB:
  - ethionamide (Trecator): 15 mg/kg/d (250 mg 3-4 tab qd) → max 1 g
  - cycloserine (Seromycin): 10-15 mg/Kg/d (250 mg 2-4 tab qd) → max 1 g
  - PAS = para-amino salicylic acid (Paser): 4 g packet bid-tid → max 12 g
  - AG = 2nd line injectables: → **not** in preg

    streptomycin 15 mg/kg/d (max 1 g) IM/ IV (off label)

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    kanamycin 15 mg/kg/d (max 1 g) IM/ IV

    capreomycin (Capastat) 15 mg/kg/d (max 1 g) IM/ IV

    amikacin (Amikin) 15 mg/kg/d (max 1 g) IM/ IV
  - FQ: levofloxacin (Levaquin) 500-750 mg qd (1250 mg off label for **MDR-TB**)

    moxifloxacin (Avelox) 400 mg qd (800 mg off label for **MDR-TB**)

Anti-TB Therapy

- 2nd line anti-TB:

  - oxazolidinones: linezolid (Zyvox) 600 mg qd-bid x 6 mon → **MDR-TB**

  - diarylquinoline: bedaquiline (Sirturo) 100 mg → **MDR-TB**
    4 tab qd x **2 w** then 2 tab tiw x **24 w**
    [alternate: 2 tab qd x **8 w**, then 1 tab qd x **18 w**]

  - nitroimidazoxazine: pretomanid 200 mg qd x 6 mon → **MDR-TB**

Anti-TB Therapy

- Drug resistant TB: resistant to INH
  resistant to Rifa
- MDR-TB: **1%** of cases:
  resistant to INH + Rifa
- XDR-TB: **0.1%** of cases:
  resistant to INH + Rifa
  + at least 1 AG (2^{nd} line injectables)
  + at least 1 FQ

Anti-TB toxicity

- INH → liver toxicity (discontinue if ALT > 5 times N)
  peripheral neuropathy (with B6 25-50 mg qd)
  metabolic acidosis & Sx disorder (INH high-dose)
- Rifa → liver toxicity (discontinue if ALT > 5 times N)
- Rifabutin → uveitis
- Rifapentine → liver toxicity
- PZA → hyperuricemia, liver toxicity
- EMB → optic neuritis
- Ethionamide → liver toxicity
- Cycloserine → confusion, suicidal thoughts
- PAS → liver toxicity
- AG → nehrotoxicity (3-5%), ototoxicity

Toxicity of FQ

- GI: nausea, vomiting, diarrhea
- CNS: seizures
- Prolonged QT: class-effect (more with sparfloxacin & grepafloxacin)
- Hepatoxicity: trovafloxacin
- Glucose homeostasis: class effect (more with gatifloxacin)
- Tendinitis (tendonitis): esp. Achilles tendon

  1% tendinitis

  0.01% tendon rupture

  (>60 years **3%**)

  (> 60 years on steroids **6%**)
- Rash: gemifloxacin (**factive)**: 30% estrogen-mediated rash

  (women < 40 years or women on estrogen)
- In the past: not used in children < 16 years (cartilage damage)

  Now: used for children

Toxicity of Linezolid

- tongue discoloration (if used > 2 weeks)
- BM suppression (if used > 2 weeks)
- peripheral neuropathy (if used > 2 weeks)
- optic neuropathy (rare, irreversible)
- serotonin syndrome (with SSRI)

Shorter Treatment Regimen for drug-susceptible TB

- recent clinical trial conducted by CDC & NIH (2020)

  → new **4-mon** regimen for treatment of drug-susceptible pulmonary TB is non inferior to standard **6-mon** regimen

Table 1. Two Drug Regimens for Drug-Susceptible TB[1]

Regimen	Intensive Phase	Continuation Phase
Standard 6-Month Treatment	Rifampin 600 mg + Isoniazid 300 mg[2] + Ethambutol 800-1600 mg[3] + Pyrazinamide 1000-2000 mg[4] once/day x 8 wks	Rifampin 600 mg + Isoniazid 300 mg[2] once/day x 18 wks
Rifapentine-Based 4-Month Treatment	Rifapentine 1200 mg + Isoniazid 300 mg[2] + Moxifloxacin 400 mg + Pyrazinamide 1000-2000 mg[4] once/day x 8 wks	Rifapentine 1200 mg + Isoniazid 300 mg[2] + Moxifloxacin 400 mg once/day x 9 wks

1. SE Dorman et al. Contemp Clin Trials 2020; 90:105938.

2. Pyridoxine 25-50 mg once daily is also recommended to decrease the risk of isoniazid-induced neuropathy.
3. Dose is based on body weight (<55 kg: 800 mg; 55-75 kg: 1200 mg; >75 kg: 1600 mg).
4. Dose is based on body weight (<55 kg: 1000 mg; 55-75 kg: 1500 mg; >75 kg: 2000 mg).

Anti-MOTT

Pulmonary/lymphatic/ disseminated: **MAC** (MAI)

treatment: **2-4** meds, for **12-18** mon:

1st choice: **clarithromycin** (alternate: azithromycin)

2nd choice: **ethambutol (EMB)**

3rd choice: **rifabutin** (alternate: rifampin)

4th choice: **FQ** (levofloxacin or moxifloxacin)

amikacin IV/IM

most widely used (**clarithro + EMB + rifabutin**)

Anti-MOTT

Pulmonary

Kansasii: **INH + Rifa + EMB** x 12 mon (**no** PZA)
also **clarithro** + **FQ**

Abscessus: **2** IV Abx + **2** oral Abx :
IV : **amikacin, tigecycline, imipenem** x 1 mon
PO : **clarithro, FQ , doxy, linezolid** x 12 mon

Fortuitum: **1** IV Abx + **2** oral Abx :
IV : **amikacin, imipenem** x 1 mon
PO : **clarithro**, **FQ , doxy, Bactrim** x 12 mon

Xenopi: **Clarithro** + **Rifa** + **EMB** x 12 mon

Genavense: **Clarithro** + **Rifa** + **FQ** or **Doxy** x 12 mon

Gordonae: mostly contaminant
Clarithro + EMB + FQ x 12 mon

Anti-MOTT

Cutaneous

Hemophilum: **Clarithro** + **FQ** or **Doxy or rifabutin or rifampin** x 4-6 mon

Marinum: **Clarithro** + **FQ or Doxy or rifabutin or rifampin** x 4-6 mon

rapid-grower: Fortuitum/ Chelonae / Abscessus:

Clarithro + **FQ** or **Doxy** x 4-6 mon

Lymphatic (lymphadenitis)

Scrofulaceum: **surgery** (95% cure rate)

or meds (clarithro + Rifa + EMB) x 12 mon

شكرا جزيلا لإصغائكم