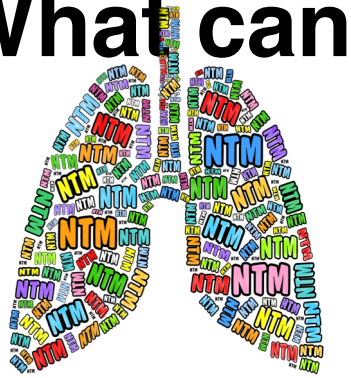
you What can do to help defeat your NTM lung disease!



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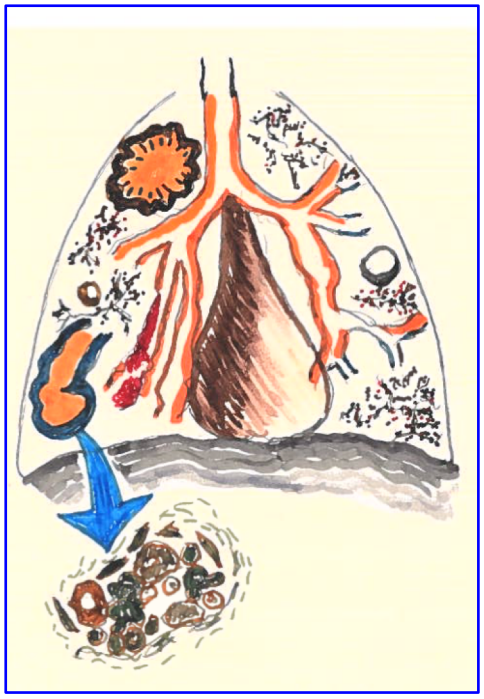


NSF-Hawaii Meeting,
February 2, 2020

2.1.2020 - 2.2.2020
LUNG DISEASE CONFERENCE, HONOLULU, HAWAI'I

My goals….

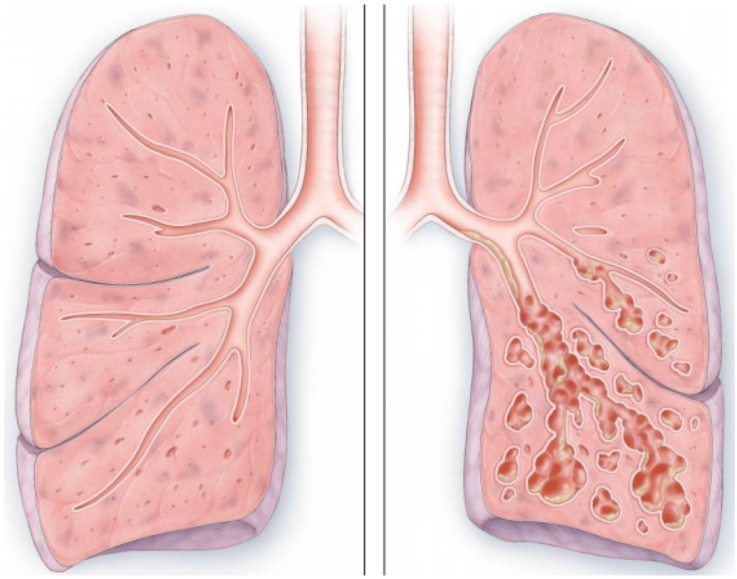
- To reveal where NTM are found and how you get exposed to them…*to help prevent a first infection or a recurrent infection*.

- To provide you hints on how best to manage your NTM lung disease…*but follow your doctors' advice or at least bring up the issue if what I say do not agree with their recommendations. But if you learn one thing that is helpful to you, it will be worth it.*

- But I learn as much from your experience so please don't hesitate to *share your thoughts or tell me if you disagree with me.*

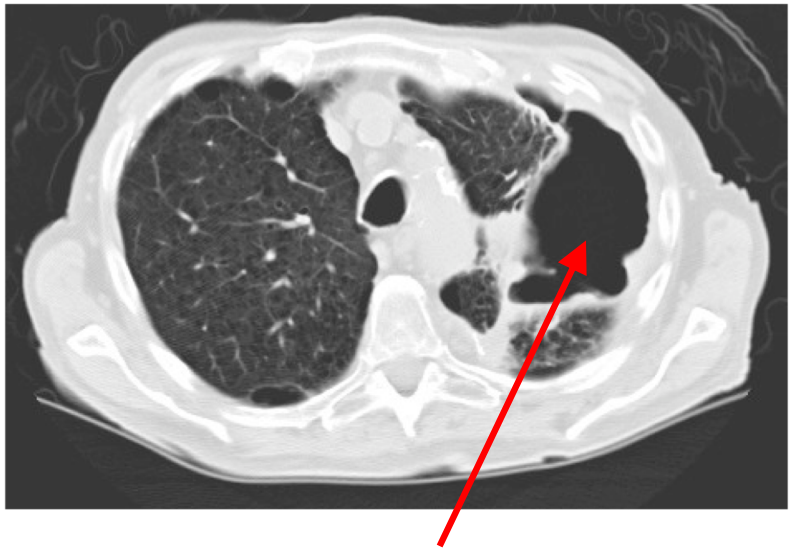
Four medical terms used by your doctors

- **#1 Bronchiectasis** – permanent dilatation of the airway, susceptible to accumulation of thick mucus and recurrent bacterial infections.



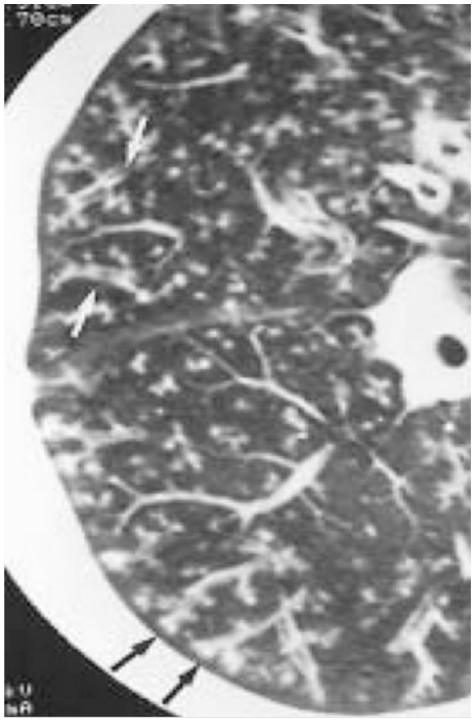
normal bronchiectasis

- **#2 Cavity** – a hole in the lung absent of viable lung tissue. A sign of lung destruction due to poorly-controlled infection and inflammation.



Large cavity

- **#3 Tree-in-bud opacities** – a sign of inflammation of the small airways = bronchiolitis



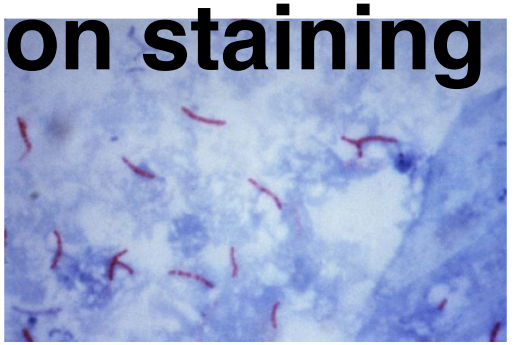
- **#4 Macrolide** = azithromycin or clarithromycin

Outline

- What are NTM, most clinically relevant NTM, and the diseases caused by them
- WHERE AND HOW DO WE GET NTM INFECTIONS?
- What are the host risk factors for NTM lung disease?
- DIAGNOSIS AND MANAGEMENT OF NTM LUNG DISEASE
- Top ten recommendations to prevent and treat NTM lung disease

What are NTM?
What are the most clinically relevant NTM?
What are the diseases caused by them?

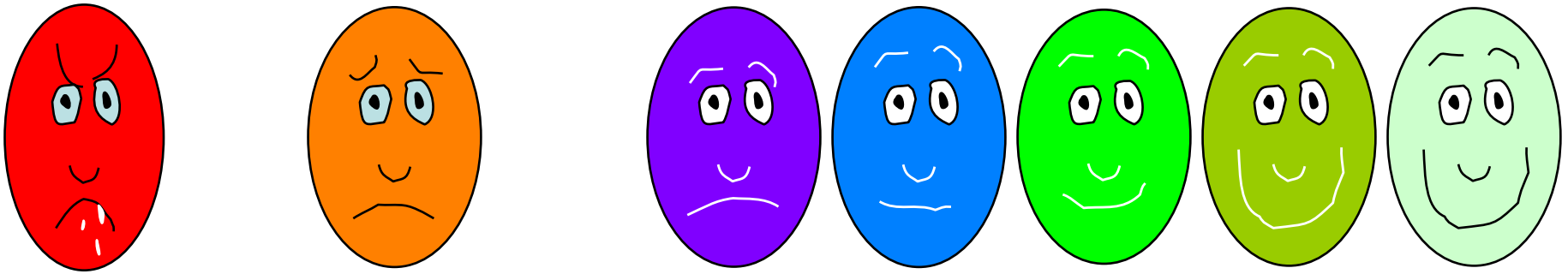
NTM are “Mycobacteria,” all of which are “acid-fast bacteria” (AFB) on staining



Tuberculosis bacteria

Leprosy bacteria

NTM (~200 species)



Harder to treat

Easier to treat

“close cousins”

“distant cousins”

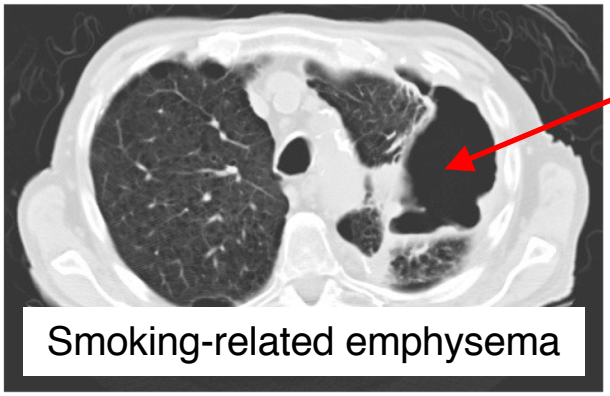
Most NTM lung disease in the U.S. are due to MAC or *M. abscessus* complex

- ***Mycobacterium avium* complex (MAC)**
  - *M. avium*
  - *M. intracellulare*
  - *M. chimaera*
  - + others

- ***M. abscessus* complex** (all used to be called "*M. abscessus*")
  - *M. abscessus* sensu stricto and *M. bolletii* (most with functional *ERM41* gene → no inducible macrolide resistance → harder to treat)
  - *M. massiliense* (non-functional *ERM41* gene → easier to treat)

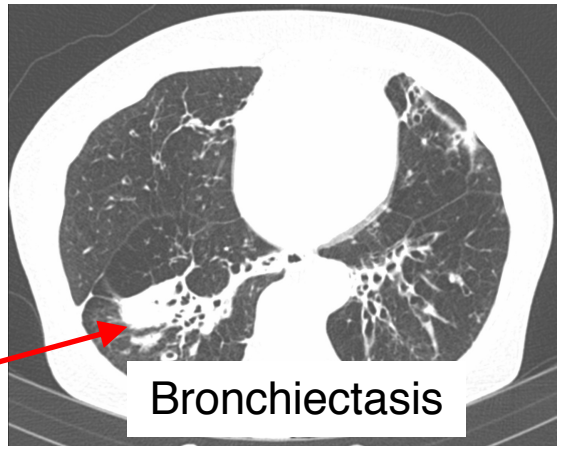
Diseases caused by NTM

- **Isolated lung disease**



NTM-associated cavity

NTM-associated bronchiectasis



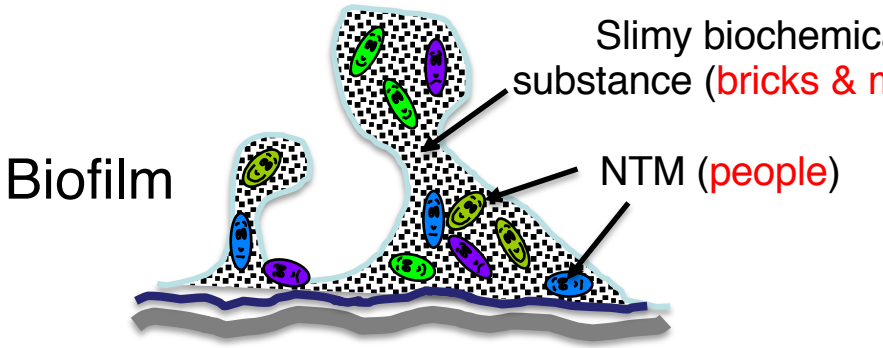
- **Skin and soft tissue infections**

- **Internal organs other than the lungs**

Where and how do we get NTM infections?

Where do we find NTM?

Soil
Water
Biofilms



Manhattan skyline

Why it is important to know where NTM are found in the environment

- **To prevent new infection** if you have a susceptible medical condition.
  - COPD / emphysema
  - Bronchiectasis
- **To prevent re-infection** (inhale it, ingest it, and/or aspirate it).
  - **Bad news: recurrence** MAC lung disease is as high as ~50% after completion of treatment.
  - **Good news**: but most recurrences are due to a NEW infection (“**re-infections**”) – 75% in one study – with a new strain of NTM rather than a **relapse** of the previous infection (25%).

Wallace RJ et al. Macrolide/azalide therapy for nodular/bronchiectatic MAC lung disease. Chest 2014

Despite controversy, showerheads are potential sources of NTM infections

Preferred

Not recommended

<u>Steps to take to minimize exposure when showering</u>:

- Raise hot water heater temperature to 130°F (140°F in Australia) and flush it yearly.
- Use showerheads that produce large diameter water streams as opposed to fine mists as that seen with water conserving models.
- Clean or replace showerheads periodically.
- Use a bathroom vent and/or open window.
- Turn on the shower for a couple of minutes and leave the room as the initial output from the showerhead may contain the greatest concentration of NTM-containing residual water / biofilms.

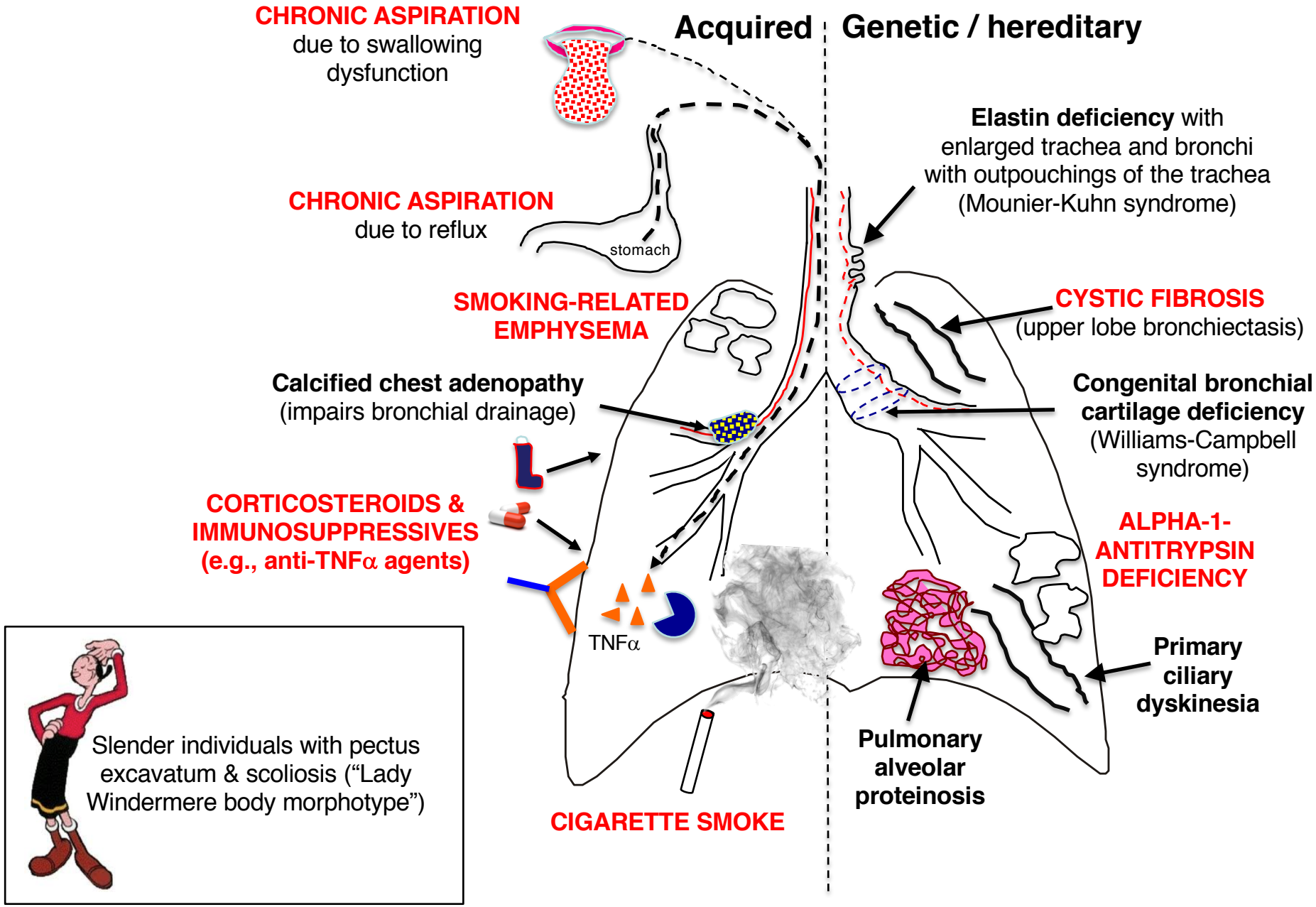
Why is potable water not safe from NTM?

- NTM can survive on very little nutrients.
- *Mycobacterium avium* complex (*MAC*) is 1,000-10,000X more resistant to chlorine than *E. coli.*
- *MAC* is more resistant to chlorine than *M. scrofulaceum*.
- *M. xenopi* and *MAC* are particularly resistant to temperatures seen in home hot water heaters.

Falkinham JO et al. Appl Environ Microbiol 2001

What are the host risk factors for NTM lung disease?

Predisposing conditions for NTM lung disease

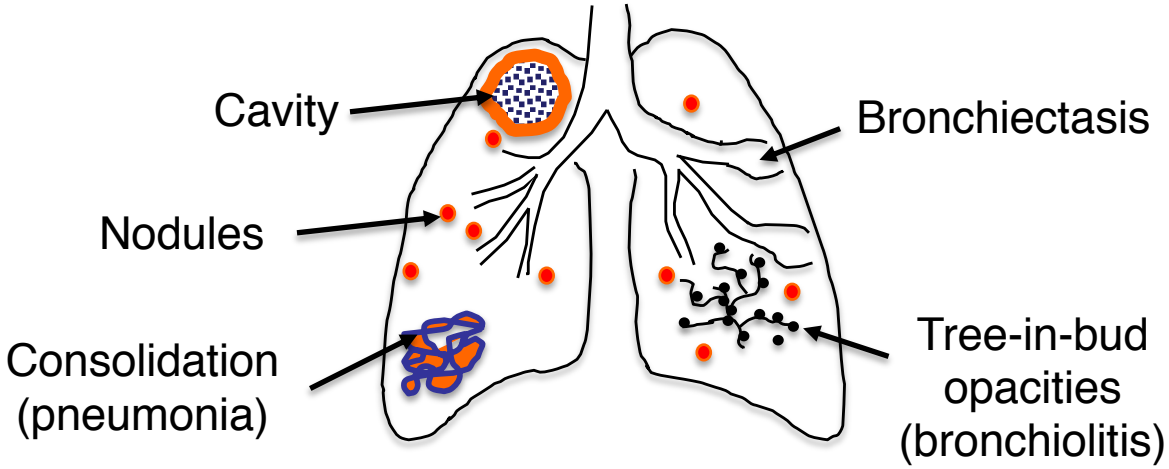


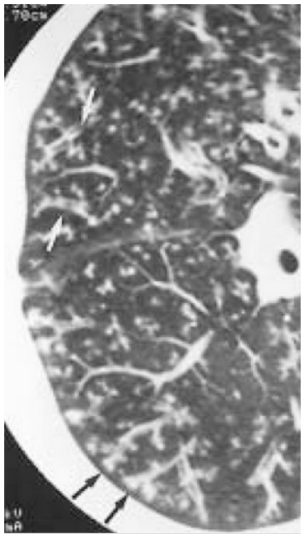
Diagnosis and management of NTM lung disease

Criteria for diagnosing NTM lung disease

1. **Clinical symptoms**: Fever, cough, sputum, fatigue, night sweats, chest discomfort, and/or shortness of breath.

2. **CT findings** compatible with NTM lung disease.

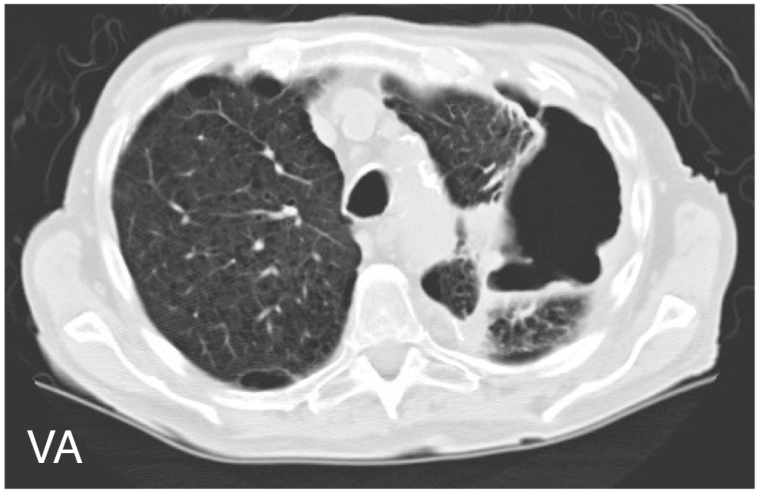




3. **Microbiological findings**:
   - ≥ two (+) sputum cultures *or*
   - one (+) bronchoscopy culture *or*
   - Lung biopsy consistent with NTM lung disease

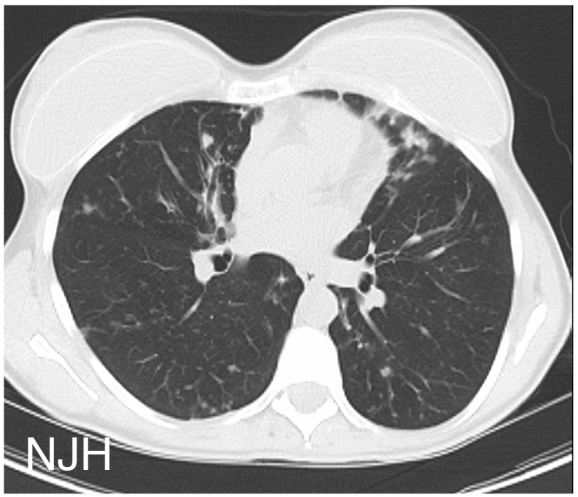
Three major radiographic patterns with NTM lung disease

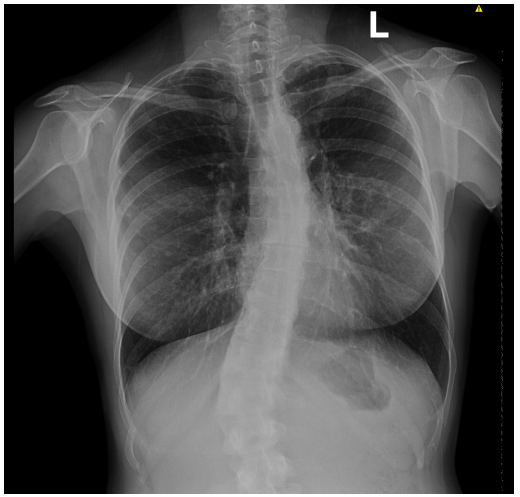
#1 Upper lobe cavitary disease



72 yo man
Underlying emphysema

#2 Nodular-bronchiectasis





41 yo previously healthy woman
"Life-long" slender body habitus & severe scoliosis

#3 Hypersensitivity ("allergic") pneumonitis ("hot tub lung")

Hanak V et al.
Respir Med 2006

What if you are told *"your sputum is positive for NTM"* ?

1. Cavity or severe bronchiectasis on CT
2. High bacterial load
3. Lots of symptoms

↓

Treat with antibiotics
+
Airway clearance
+
Avoid exposures

1. Minimal disease on CT
2. Low bacterial load
3. Little or no symptoms

↓

Airway clearance
+
Avoid exposures

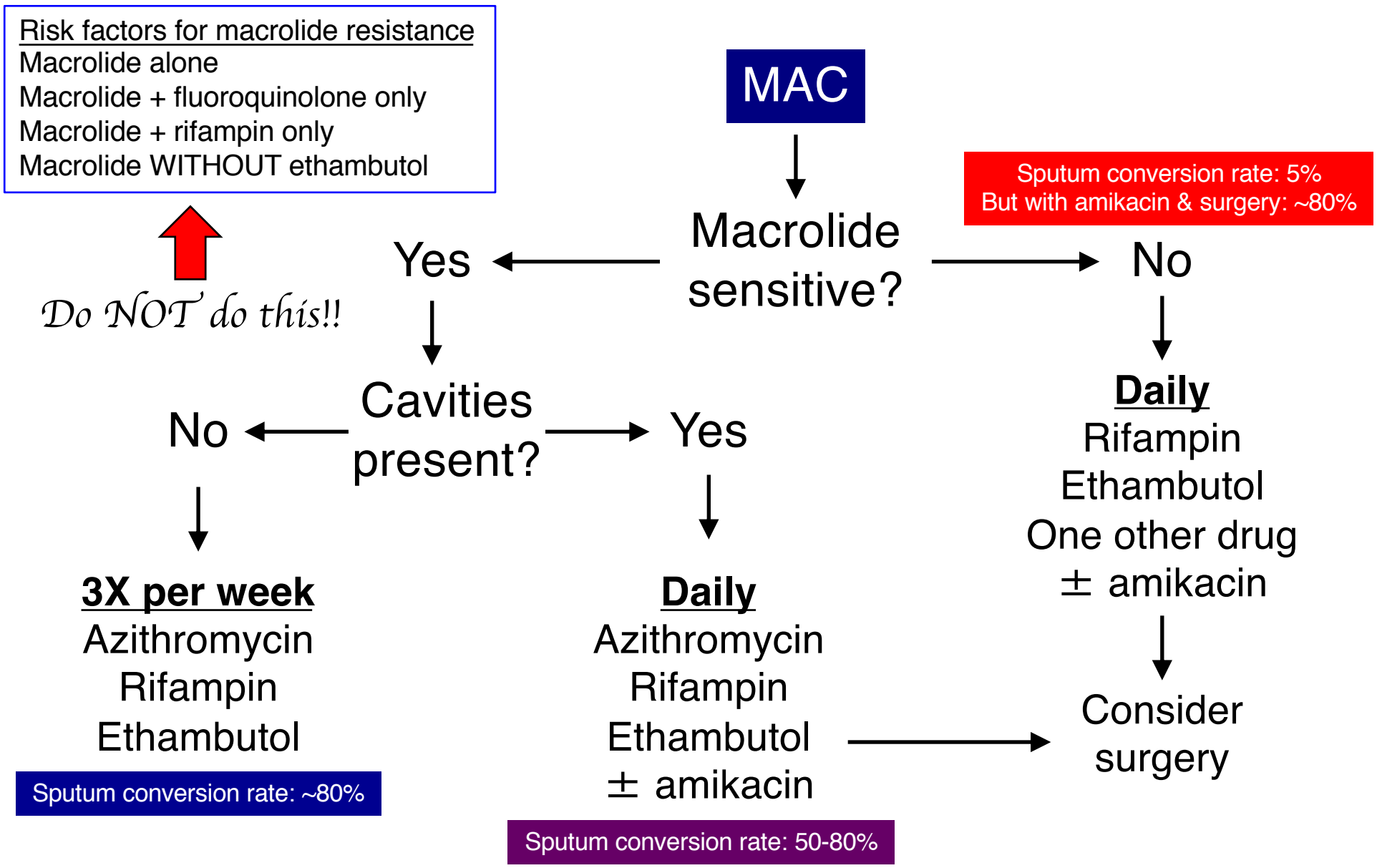
↓

Re-test sputum

↓

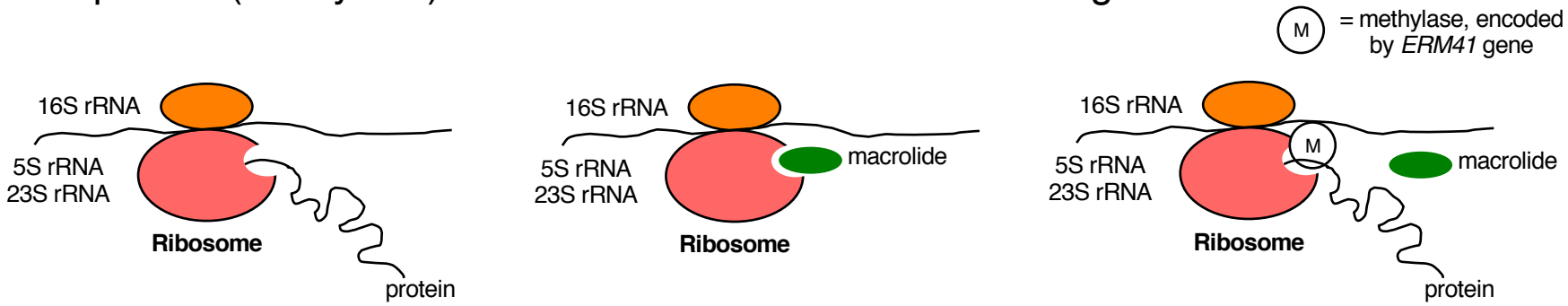
Treat if positive for NTM, radiographic progression, and/or symptoms
(in 10-15%, NTM will "disappear")

MAC Treatment Algorithm



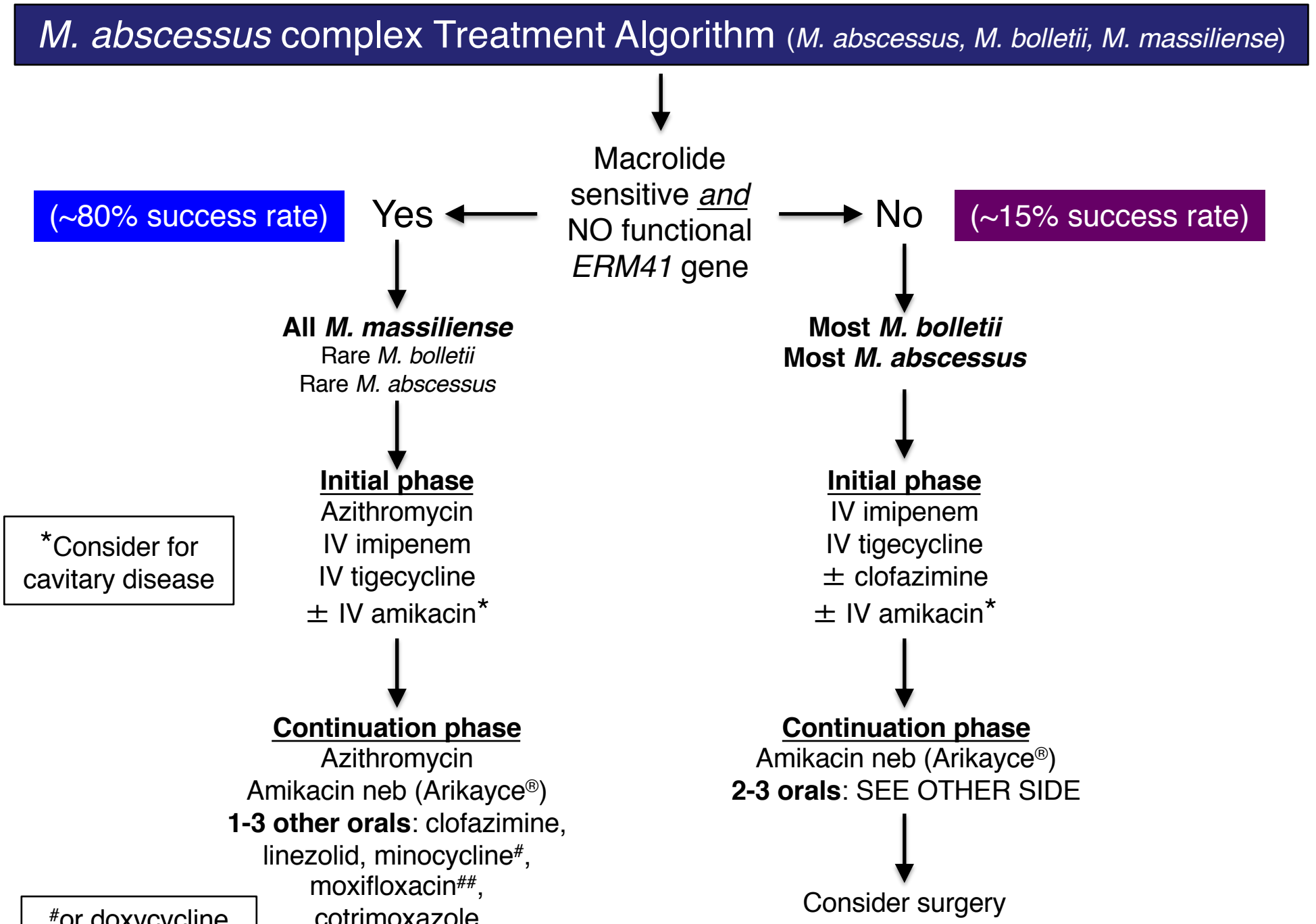
What about treatment for *M. abscessus* complex?

- As with MAC treatment, **susceptibility to macrolide (azithromycin, clarithromycin) is the most important factor in clinical outcome**.
- Macrolides bind to NTM ribosomes (organelles inside cells that make proteins) → inhibiting bacterial protein synthesis.
- **Two types of macrolide resistance**:
  - Mutational resistance to the *rrl* gene → encodes a protein that is part of ribosomes → prevents macrolide binding.
  - Inducible resistance → in the presence of a functional *ERM41* gene → encodes a protein (methylase) that interferes with macrolide binding.



<u>For the clinicians → 2 ways to determine macrolide resistance</u>:

- Incubate macrolide-susceptible *M. abscessus* for 14 days → to determine if resistance develops
- Determine if there is a C28T polymorphism of the *ERM41* gene → if so, then inducible macrolide resistance


M. abscessus complex Treatment Algorithm (*M. abscessus, M. bolletii, M. massiliense*)
Macrolide sensitive *and* NO functional *ERM41* gene
Yes
(~80% success rate)
No
(~15% success rate)
All *M. massiliense*
Rare *M. bolletii*
Rare *M. abscessus*
Most *M. bolletii*
Most *M. abscessus*
Initial phase
Azithromycin
IV imipenem
IV tigecycline
± IV amikacin*
Initial phase
IV imipenem
IV tigecycline
± clofazimine
± IV amikacin*
*Consider for cavitary disease
Continuation phase
Azithromycin
Amikacin neb (Arikayce®)
1-3 other orals: clofazimine, linezolid, minocycline#, moxifloxacin##, cotrimoxazole
Continuation phase
Amikacin neb (Arikayce®)
2-3 orals: SEE OTHER SIDE
Consider surgery
#or doxycycline
##or ciprofloxacin
Modified from BTS Guidelines
Haworth CS et al. Thorax 2017

General treatment strategies for NTM lung disease

- **Goals of treatment needs to be defined**: symptom control (drug regimen not as intense) vs. attempt to cure (more intense)….because sometimes **drug treatment may make you feel worse** than the disease itself.
- **Clarithromycin (or azithromycin)** is the most important drug for both MAC and *M. abscessus* infections.
- **Three to 4 drugs are generally required initially** and then 2-3 drugs for the long-haul.
- Generally treat for **12 months *after* three negative sputum cultures**.
- For patients with cavitary disease, **amikacin for the first 2-3 months** is often recommended.
- For those with severe localized disease, **surgery** to remove that lobe or segment may be recommended.

New formulations or repurposing available

- **Omadacycline** (IV or PO) – very good MIC against *M. abscessus* complex, *M. chelonae*, & *M. fortuitum*. May be more tolerable than IV tigecycline (?).
- **Eravacycline** (IV)
- **Cephalosporins + β-lactamase inhibitors**

Promising but not ready for prime-time

- Disulfiram (Antabuse®)
- D-cycloserine
- Nitric oxide (gas to inhale)
- Three bacteriophage cocktail for *M. massiliense* (concomitant antibiotics also given but not clear if NTM was resistant to macrolide).

Mucus clearance mechanisms: the best method is the one you do regularly!

- **Pharmacologic**

Expectorant
(e.g., guaifenesin)

Pulmozyme®
("chews up" sticky DNA – indicated for CF patients only)

Hypertonic saline

Inhaled mannitol
(a sugar to help liquify sputum)

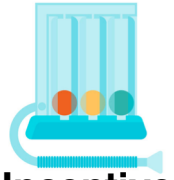
- **Non-pharmacologic**

Aerobika®

Acapella®

High-frequency oscillatory vest

Chest physiotherapy



Incentive spirometry

Huff cough

Hydration

Exercise

Hypertonic saline (HS)

- Usefulness of HS is well-established in cystic fibrosis.
- **Mechanism of action**: helps hydrate mucous, improves mucociliary clearance, stimulates cough, & some antimicrobial effect.
- **Potential benefits**: enhances expectoration of sputum, reduces sputum stickiness, reduces exacerbation of bronchiectasis, improves lung function, and enhances quality of life.
- **Dose**: 3% or 7% saline as a nebulizer once or twice daily.
- **Side effects**: throat irritation, cough, & bronchoconstriction (wheeze).

Carrol M & Martinez-Garcia MA. Nebulized hypertonic saline in noncystic fibrosis bronchiectasis: a comprehensive review. Ther Adv Respir Dis 2019; 13:1-15.

Use of the Acapella® valve

- Acapella® combines both positive airway pressure and airway vibrations to mobilize secretions and can be used in virtually any position.
- Acapella® is color-coded (DH green for high-flow and DM blue for low-flow; most adults should use the green one).
- **Use of the Acapella® valve**
  - Assure proper setting of the resistance dial on the end of the Acapella® valve. Start at the mid-resistance point and rotate toward + or - to increase or decrease resistance as tolerated. Adjust resistance so that you can exhale for at least 3 sec.
  - Sit up with good posture to use the Acapella although various positions may be required for optimal drainage of secretions.
  - Place the Acapella® mouthpiece in the mouth. Seal lips tightly around the mouthpiece.
  - Take in a bigger than normal breath and hold for 2-3 sec.
  - Exhale actively (NOT forcefully) until the flutter sound ceases.
  - Repeat 10X → 3 huff coughs → a big cough to bring out the sputum.
  - Repeat each session 2-4X per day.

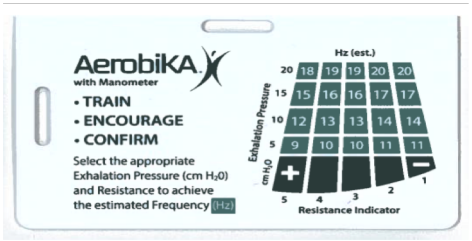
Acapella®

- Clean the Acapella® at the end of the day in liquid dish detergent, rinse and dry.
- Disinfect Acapella® weekly by removing the mouthpiece from the body and soak in 70% rubbing (isopropyl) alcohol for 5 min or 3% hydrogen peroxide for 30 min. Rinse thoroughly with water and drain/dry in a vertical position.

Use of the Aerobika®

- Best to be trained by a Respiratory Therapist before use.
- **Use**:
  - Place mouthpiece in mouth.
  - Inhale bigger than normal breath and hold ~3 seconds.
  - Adjust resistance so that one is able to ~3 seconds.
  - Repeat 10X → 3 huff coughs → a big cough to bring out the sputum.
  - Repeat each session 2-4X per day.
- Aerobika® may come with a **manometer**, which gauges whether the expiratory blow is adequate. The manometer contains a green zone (5-20 cm H_2O), yellow zone (20-40 cm), and red zone (40-60 cm). It is recommended to stay within the **GREEN ZONE**; *e.g.*, 10-15 cm H_2O pressure.
- Based on the chart below, at a resistance setting of "3", if one exhales to 10-15 cm H_2O pressure, this results in an airway beating frequency of 13-16 Hz.
- Aerobika® may be used in-line with a nebulizer that contains a bronchodilator or hypertonic saline.

Aerobika with manometer



Aerobika with in-line nebulizer

Nutrition and NTM

- **Thin individuals are more susceptible** to NTM lung disease. Thus, maintain ideal or closer to ideal body weight.
- **Eat healthy fats** (*e.g.*, avocados, olive oil, fish fat) and **eggs**.
- **Mirtazepine** is a sleep aid that also increases appetite.
- Make sure 25-OH vitamin D level is between 30-60 ng/mL.

Gastroesophageal reflux

- **Definition**: reflux of stomach contents into the esophagus and even higher.
- **Significance**: can damage the esophagus and spill into the lungs.
- Antacids decrease stomach acid but does not prevent reflux.
- Sleep with head-of-bed elevated at 30^{o} or higher.
- **Drugs that can worsen reflux**: albuterol, oxybutynin, Benadryl®, tricyclic antidepressants, calcium channel blockers, nitrates, opioids, progesterone, quinidine, benzodiazepines, and theophylline.
- **Foods that can worsen reflux**: coffee, chocolate, caffeine, alcohol, peppermint, garlic, onions, fatty-spicy foods, citrus fruits, and tomatoes.

Avoid gardening but if you must…

- Dampen soil first to lessen aerosolization…
- Avoid gardening on windy days.
- Avoid mowing lawns.
- Pot plants outside on non-windy days.
- Wear N-95 masks if exposure to soil is significant.

Ways to prevent superimposed respiratory infections…

- Avoid crowds / carry and use hand sanitizers.
- **Use your elbow to**: greet people (*"I don't want to pass any germs to you"*), press elevator buttons, push subway turnstiles, and open doors.
- Do not touch your nose / eyes after being in public places without first cleaning hands.
- Keep up to date on influenza, pneumococcal, and pertussis vaccines.

When prescribed multiple inhaled therapies, recommended order of use…

1. **Short-acting bronchodilator**: albuterol or levalbuterol ± ipratropium
2. **Hypertonic saline**
3. Vibratory vest
4. Pulmozyme® (DNAse) – indicated for only CF patients
5. Inhaled corticosteroids*
6. Long acting bronchodilator
7. Inhaled antibiotics

*Several formulations have 5 + 6 combined in one inhaler

* Inhaled corticosteroids have been associated with increased NTM lung infection

Top Ten Recommendations

1. Avoid inhaling aerosols of soil and water.
2. Raise hot water heater temperature to 130^{o}F and flush yearly.
3. Take measures to prevent stomach reflux.
4. Avoid cigarette smoke exposures.
5. Eat healthy fats in moderation, keep vitamin D at good levels and keep active.
6. Take antibiotics as directed.
7. Do **airway clearance religiously**.
8. Join NTM Support Groups and educate yourself and others about various aspects of NTM lung disease (NTMir® resource).
9. Find **medical professionals with experience, enthusiasm, and patience** to treat NTM lung disease.
10. Keep an orderly record of your medical test results and key events.