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PULMONARY, CRITICAL CARE AND SLEEP MEDICINE

NON-TUBERCULOUS MYCOBACTERIA

INTERACTION WITH THE EXTERNAL AND INTERNAL ENVIRONMENTS

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October 2020

FINANCIAL DISCLOSURE

- **Insmed: Speakers bureau**

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GOALS OF TALK

- Why environmental factors are important in understanding the disease
- Understand why those factors are important in assessing the individual patient
- Gain perspective on how the *personal (external and internal)* environment is the pivotal factor in acquiring the infection and treating the infection
- Emphasis on Biofilm in environment, disease and treatment
- ****Address varying levels of audience experience with NTM. Some review for the "veterans"

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SEQUENCE OF REACTING TO THESE ORGANISMS FOR TODAY

- **Environment – A & A**
  - **– *Avoidance***
  - **– *Acquisition***
- ***Personal* predispositions – Research updates**
- **Non-pharmacologic *management* – Airway clearance**
- ***Medication* – Old and new approaches**

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LARGE ENVIRONMENT TO LOCAL ENVIRONMENT

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Geographic Distribution of NTM identified among Clinical Isolates in the US, 2009-2013

– Spaulding, et al. Annals ATS 2017

- **Significant geographic variation exists in the distribution of NTM species in the US**
- **M. avium complex much more common in the South**
- **M. abscessus in the West**

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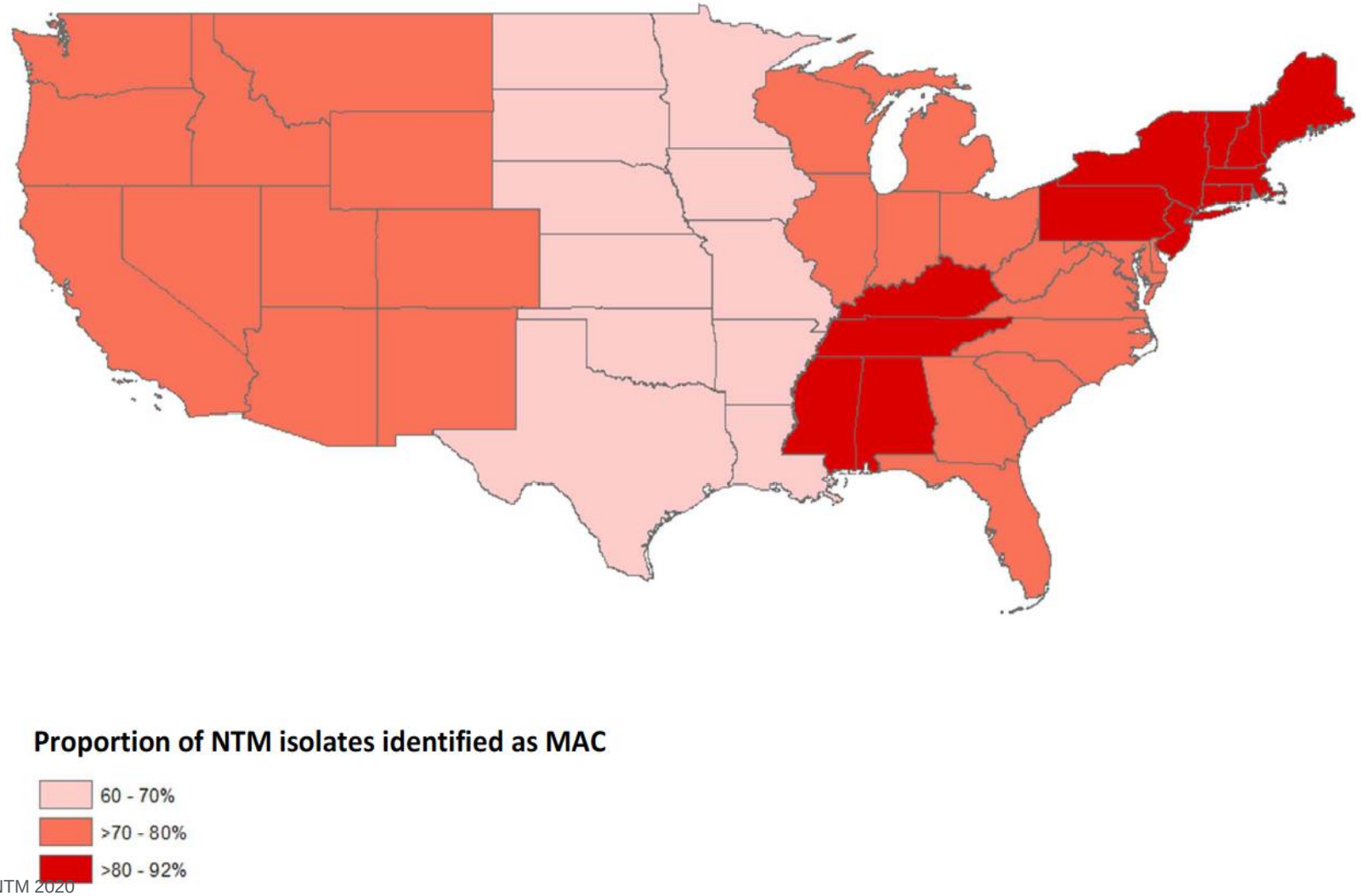
Distribution of MAC by United State geographic region in *Premier*™ Healthcare Database, 2009-2013.



RELATIVE RISK OF CLUSTERS OF PULMONARY NTM AMONG MEDICARE BENEFICIARIES

- **High risk**
  - Highlands, FL 1.9
  - Santa Barbara, CA 2.0
  - New York, NY 2.7
  - Kalawao, HI 3.7
  - Plaquemines, LA 6.5
- **Low risk**
  - Washington, RI 0.5
  - Iosco, MI 0.4
  - Roane, WV 0.4

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EVAPOTRANSPIRATION

“The process by which water is transferred from the land to the atmosphere by evaporation from the soil and other surfaces and by transpiration from plants”

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LOCAL ENVIRONMENT

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PREVALENCE: PROXIMITY TO WATER CF CHILDREN

Bouso et al. 2016

- **Retrospective chart review 65 children in Florida**
- **21(32.3%) had 2+ positive sputum cultures NTM**
- **3 year follow-up**

- **CF patients who lived within 500 meters of water were 9.4 times more likely to have NTM**

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SHOWERHEAD UPDATE
Annals ATS 10.23.2019

- **Purpose: Test associations between MAC pulmonary disease (MAC-PD) and NTM colonization of five potential point-of-use sources of pathogen exposure in homes**

- **Washington and Oregon residents *clinically diagnosed* MAC-PD**
- **Population age, gender, population matched controls**
- **Samples:**
  1. **Bathroom faucets**
  2. **Kitchen faucets**
  3. **Shower aerosols**
  4. **Indoor soil**
  5. **Outdoor soil**

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SHOWERHEAD UPDATE (cont.)
Annals ATS 10.23.2019

- **Findings: More NTM colonization in shower aerosols collected from case homes compared to controls**
- **Other point-of-use sites did NOT exhibit this association (e.g. kitchen)**
  - **Other studies found otherwise**
- **The FIRST case-controlled study between human health and NTM exposure in residential environmental environments**
- ****This study did not match DNA strains of shower head DNA to patient secretion DNA**
- **Thus other considerations including the overall home environment that promotes NTM growth, etc. to be considered**

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M. avium in Community and Household Water

Lande, Wallace, Falkinham, et al. 3/2019

- Investigated MAC colonization of household plumbing in suburban Philadelphia
- Compared MAC isolated from plumbing biofilm with MAC isolated from patient respiratory specimens
- M. avium was recovered from 81% of 37 households including 91% of M. avium patients
- For 52.4% of those patients with M. avium disease, the recovered plumbing organism was the same genotype as that recovered from the respiratory isolate (sputum) (but not all)
- 6 genotypes were recovered from the majority of households and patients

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GLOBAL DISTRIBUTION OF MYCOBACTERIA IN SHOWERHEADS

Gebert, Adjemian, et al 2018

- Citizen scientists collected specimens from showerhead biofilm samples
- 665 households across the United States and Europe
- Both culture-dependent and non culture-dependent methods were used to isolate mycobacteria (Stay tuned for Dr. Segal)
- Mycobacteria were far more abundant in showerheads receiving water from municipal water sources than from well water
- U.S. households were significantly higher in NTM isolates than European (Denmark and Spain)

- Differences in regional geography as well as in water chemistry influenced the isolates

GLOBAL DISTRIBUTION OF MYCOBACTERIA IN SHOWERHEADS

- **Those regions of the USA that are traditionally identified with relatively high abundance of known mycobacteria in the showerheads generally overlapped with the regions that have a higher-than-average prevalence of NTM lung disease**

- **Conclusion: Mycobacterial distribution in showerhead biofilms are often predictable from household location and water chemistry**

- **This understanding of NTM transmission and dynamics may help to reduce exposure from these increasingly prevalent organisms**

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NIH 2012 – Adjemian

- **ASIAN- PACIFIC > WHITES**
  - **228 VS. 116/ 100,000**
- **WESTERN STATES > EASTERN**
  - **149 VS 131**
- **WOMEN > MEN**
  - **1.4 TO 1.0**

Within the same environment, *intrinsic* factors are operative as well

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WHY SHOWERHEADS?

SAPROZOIC ORGANISMS

- **OPPP's: Opportunistic Premise Plumbing Pathogens**
- **Grow within biofilms and sediments, *not freely***
- **May be viruses, bacteria, fungi and protozoal diseases**
- **Not all such organisms are pathogenic**

Need to understand biofilms to prevail

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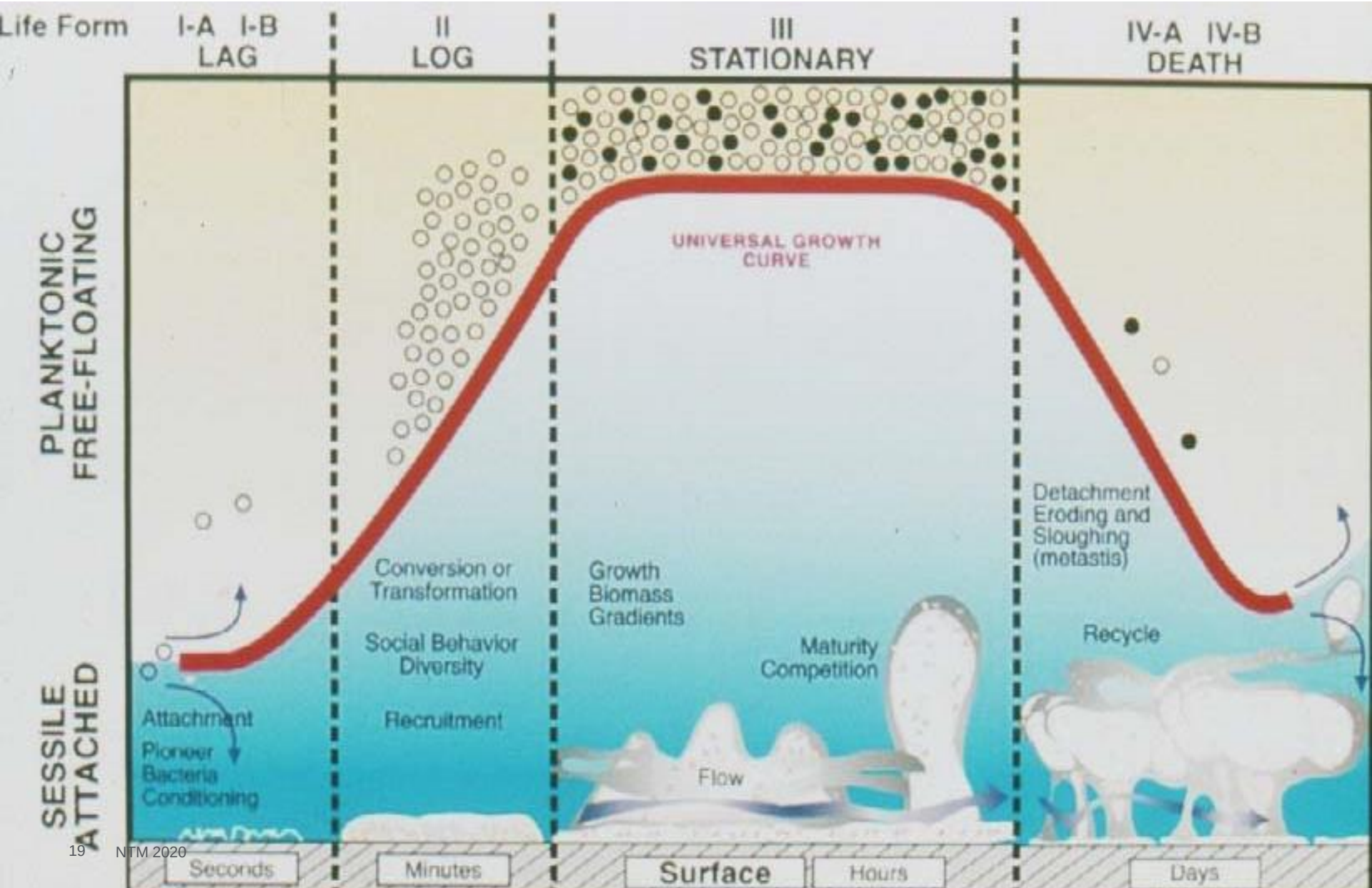
MICROBIAL LIFE FORMS CYCLE



BACTERIAL BIOFILM

- During biofilm assembly, bacteria secrete a substance (matrix) with polysaccharides, lipids and nucleic acids
- This matrix material allows for a biofilm architecture which is three dimensional
- Bacteria in biofilm achieve maximal replication rate
- Far higher concentrations of antibiotic required to kill biofilm bacteria than free-swimming bacteria of same strain (10-1000X)
- When nutrients run out, bacteria can rapidly disperse and colonize better locations where conditions are more favorable once more

- Very sophisticated system!!!

MYCOBACTERIAL BIOFILM

- **Mycobacteria are "Biofilm Pioneers"**
- **Mycobacteria adhere to and form biofilm in saprozooic (plumbing) settings and in airways, bronchial tubes, cavities and bronchiectatic airways!**
- **Mycobacteria "buddy up" with co-pathogens, including Pseudomonas in these airways**
- **Mycobacteria appear to become even LESS dependent on nutrients, oxygen and MORE resistant to chlorine**
- **They appear to be more antibiotic resistant in biofilm setting**

CHLORINE RESISTANCE OF OPPP'S vs. E.Coli

- **Pseudomonas – 21 – fold**
- **Legionella – 83 - fold**

M. avium – 567-fold (!!!!!)

– **Resistance is increased in biofilm state**

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BIOFILM AND NTM

M. abscessus less adherent than
M. avium and M. intracellulare on surfaces

BIOFILM IN NTM DISEASE

- Until now, have discussed NTM biofilm in the environment. Now in the patient
- NTM LD (lung disease) often occurs in patients with underlying disease (old TB, silicosis, bullous disease, lung cavities) Fibrocavitary
- NTM form biofilm in the cavities and progress to cause disease
- This is more recently recognized in 1980's-90's re Lady Windermere Syndrome, including chronic bronchiectasis and Cystic fibrosis. Nodular bronchiectatic
- ***Mycobacterial biofilms have recently been identified in samples from lung cavitary disease
- Experimental data have shown that biofilm is important in the ability of NTM to invade bronchial epithelial cells

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BIOFILM IMPACT IN DRINKING WATER SYSTEMS
IMPLICATIONS FROM BACTERIAL ANTIBIOTIC RESISTANCE TO NTM
Zhang, et al . 2018

- Increasing awareness of importance of antibiotic resistance
- This appears to be an emerging problem in drinking water distribution systems and not only in hospitals, ICU's and locations where antibiotics are used (in abundance)
- The bacteria were tested for resistance to four common antibiotics over one year.
- The water was tested for these bacteria at the public water source (reservoir, etc.) and again at the outflow user source (home faucet, etc.)

- This appears to be explained by the acquisition of antibiotic resistance(ARB=Antibiotic Resistant Bacteria) in the biofilm and the biofilm detachment of these organisms which are in turn released into the water system downstream, at the "consumer" location, e.g. faucet, showerhead

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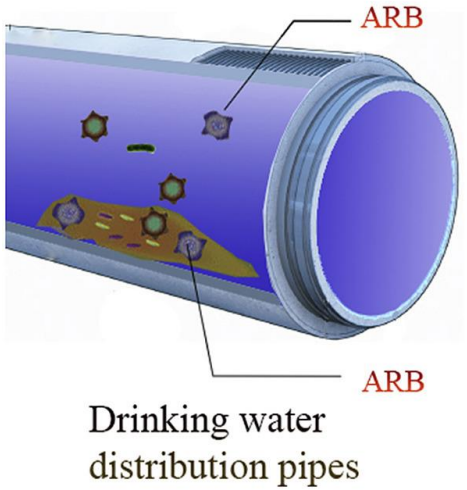
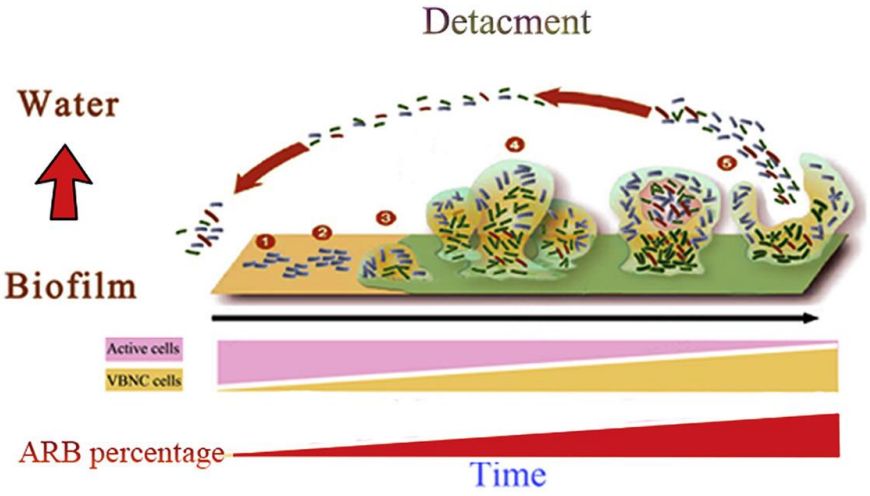
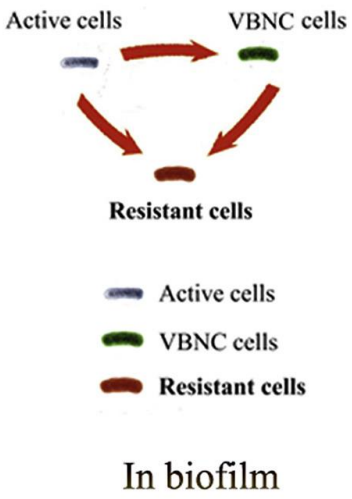
BIOFILM







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MYCOBACTERIUM ABSCESSUS AND BIOFILM

Rojony 2020

- M. abscessus appears to less surface adherent than MAC
- When M. abscessus does enter a biofilm state, it is more likely to "cord" and it is then more likely to transform from the smooth to rough colony state in the lab. That is more virulent form of M. abscessus!
- Since antibiotics generally work against aerobically growing and metabolically active bacteria, treatment is far less successful against the biofilm state
- The organism upregulates ten common metabolic pathways, changing the characteristics of the bacteria against which antibiotics have their effect

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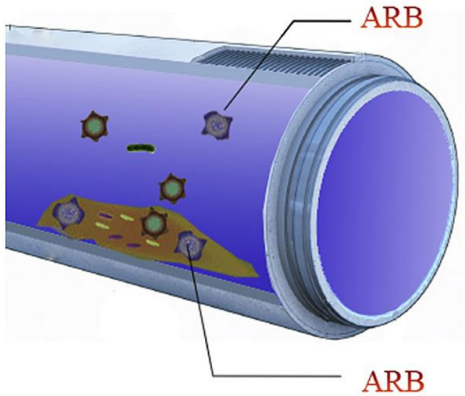
M.abscessus and Biofilm

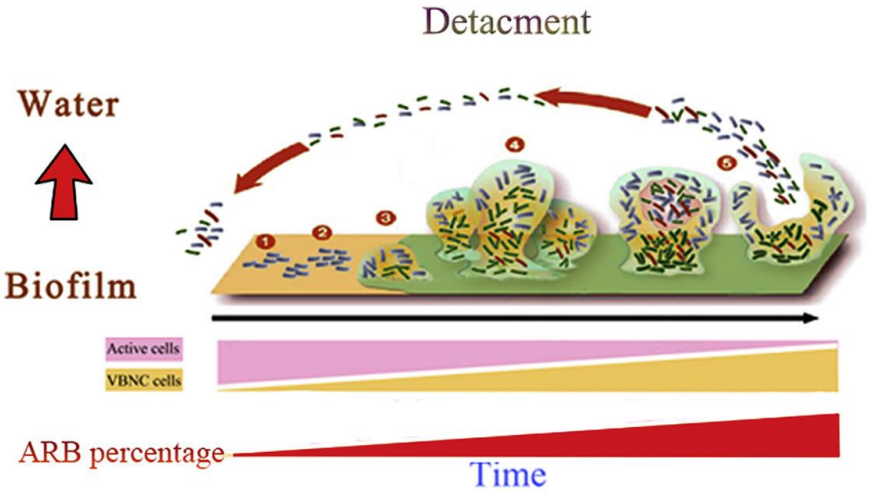
- These changes, including in the composition of the fatty cell wall as well as in the internal workings of the cell, make biofilm-dwelling M. abscessus yet harder to deal with medically

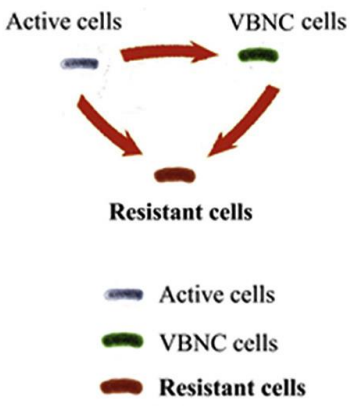
- Does any of the previously described in vitro Biofilm organism shedding occur as well????

BIOFILM



Drinking water distribution pipes





In biofilm

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MAC RECOVERY FROM SOIL

- **In Europe, soil (indoor and outdoor) is a more prevalent reservoir of MAC than are tap water in North America and bathrooms in Japan**
- **Dust aerosolized in homes in Europe where soil contained MAC grew and aerosolized MAC**
- **Hypothesis: Individuals may carry MAC-containing dust from environment to environment**
- **New niches may form in this way**

NTM: IMPORTANCE OF BETTER PREVENTION

- **The infected stay infected**
- **The infected are persistently infected**
- **The infected are repeatedly infected**

Worthwhile identifying *source* of infection

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CONCLUSIONS FOR NOW

- Environmental **AND** host factors
- Water and water ***vapor*** involved
- Aerosol
- **Biofilm**

Uncertain which individual exposure(s) and behaviors are most involved

CLEAR THAT BIOFILM IS CENTRAL!!!

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THANK YOU

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