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ENVIRONMENTAL SOURCES FOR NON-TUBERCULOUS MYCOBACTERIAL INFECTION

WHERE IS IT?

Pulmonary disease

Non-HIV Population

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FINANCIAL DISCLOSURE

- **Insmed: Speakers bureau**

GOALS OF TALK

- **Understand how understanding environmental factors is 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**
- **Emphasis on Biofilm in environment, disease and treatment**
- ******Address varying levels of audience experience with NTM**

SEQUENCE OF REACTING TO THESE ORGANISMS FOR TODAY

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

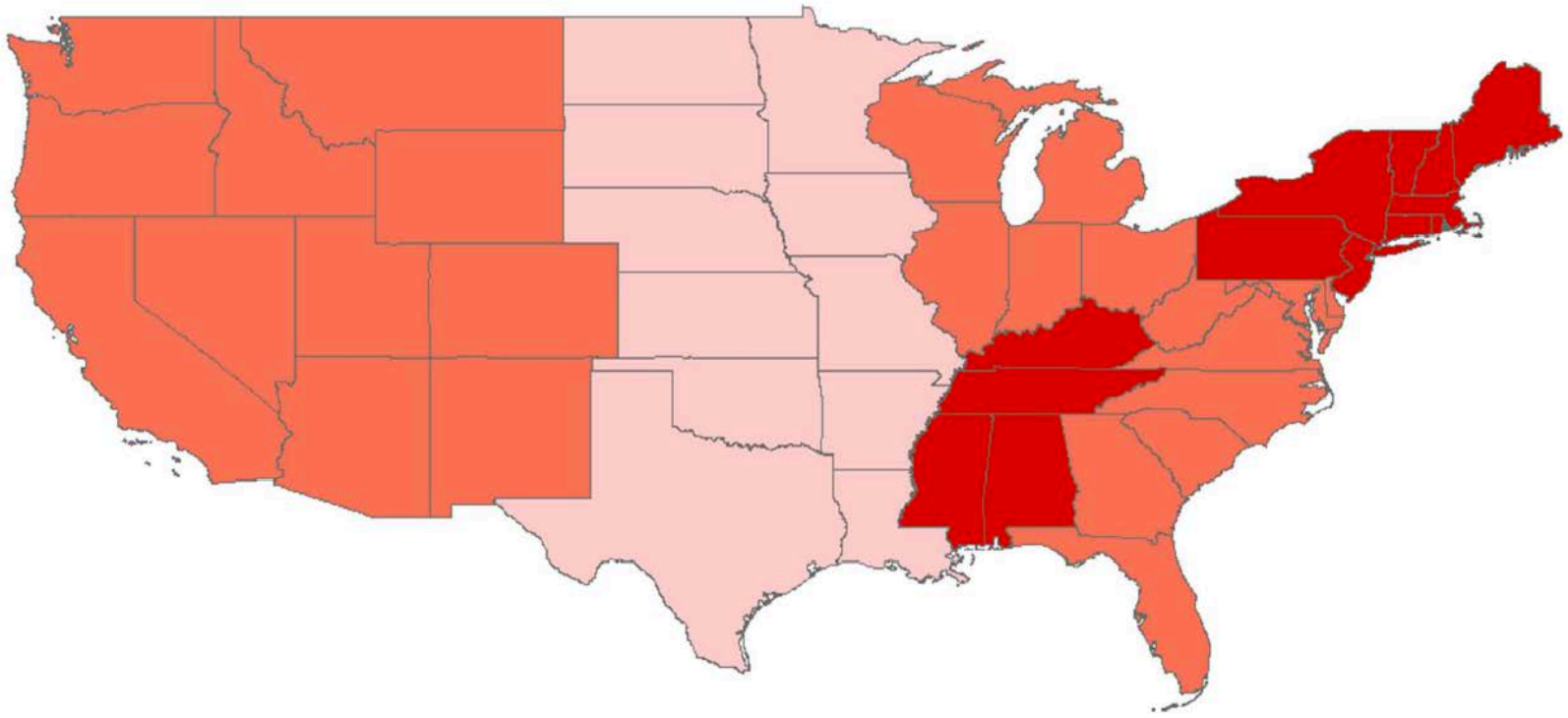
LARGE ENVIRONMENT TO LOCAL ENVIRONMENT

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**

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



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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

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”

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

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**
- **Other significant factors included hx of Aspergillus OR Pseudomonas**

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:**
  - **Bathroom faucets**
  - **Kitchen faucets**
  - **Shower aerosols**
  - **Indoor soil**
  - **Outdoor soil**

SHOWERHEAD UPDATE
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**
- **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**

EPIDEMIOLOGY: HOSPITAL ACQUIRED INFECTION

- **M. chimaera isolated from multiple patients who had undergone bypass procedures**

- **Is it possible that non-sterile water used in hospital heating and cooling devices can cause contamination and clinical infection**

SAPROZOIC ORGANISMS

- **OPPP's: Opportunistic Premise Plumbing Pathogens**
- **Grow within biofilms and sediments, *not freely***
- **May be viruses, bacteria, fungi and protozoal diseases**
- **Legionella grows *within* free-living protozoa that reside in the biofilm**
- **Not all such organisms are pathogenic**

Need to understand biofilms to prevail

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SAPROZOIC ORGANISMS CONTROL MEASURES

- Central water reservoirs
- Regional water distribution systems
- Individual homes
- Hospitals
- Public spaces

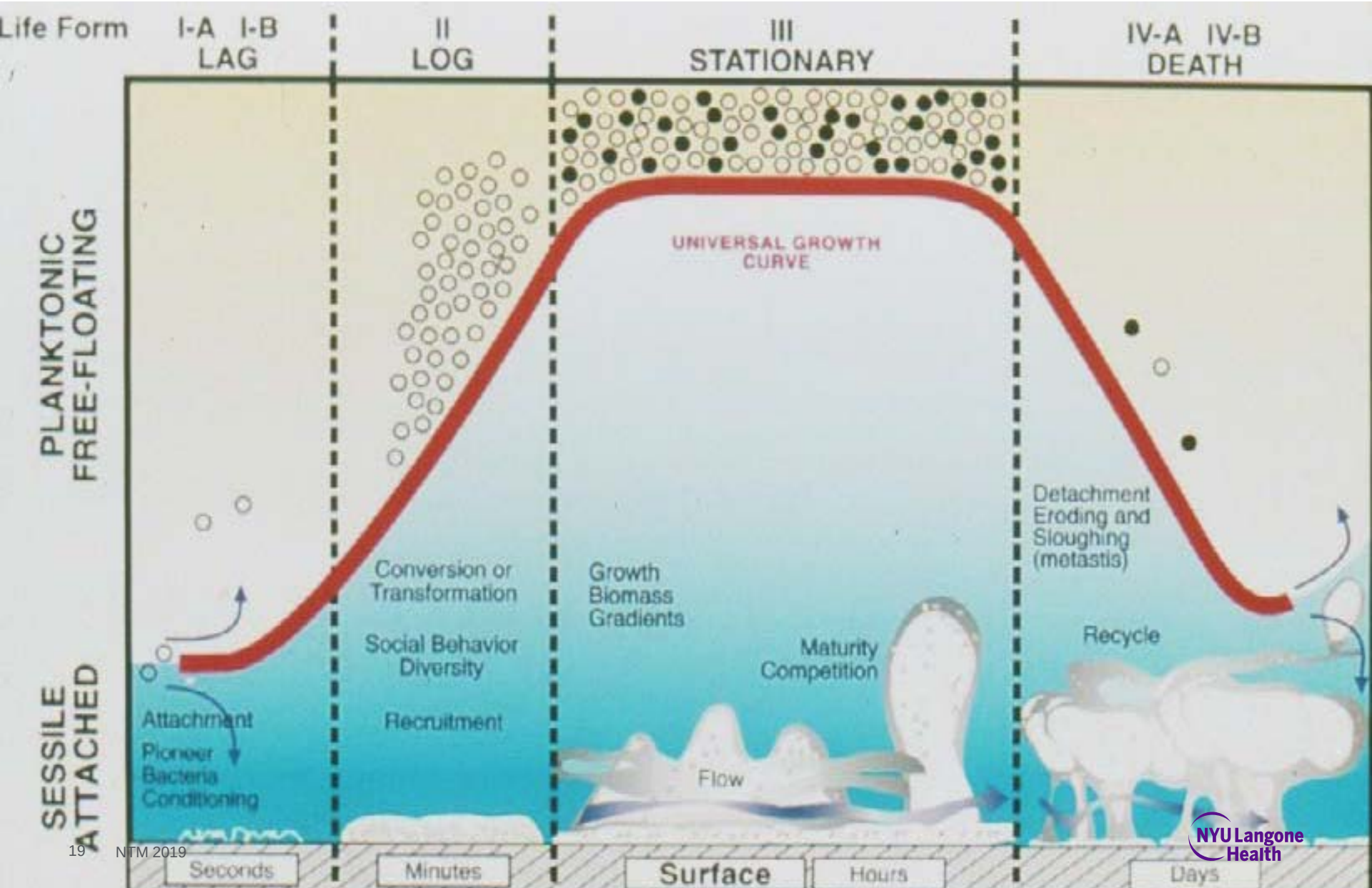
M. avium AS OPPP

- M. avium grows very slowly (1 generation per day) vs. 40 minutes for average bacteria (e.g. E. coli)
- Adheres to biofilm on pipe surfaces
- It is not washed out by water flow
- Chlorine resistant
- Heat resistant
  - 90% survive at 125F for sixty minutes
  - Able to survive in hot water heaters
- Survive stagnancy
  - Able to grow in 6% and 12% oxygen as well as 21% oxygen (room air)
- Survives/ flourishes in amoebae rather than being killed by amoebae in water systems

CHLORINE RESISTANCE OF OPPP'S vs. E.Coli

- **Legionella – 83–fold**
- **Pseudomonas – 21 – fold**
- **M. avium – 567-fold (!!!!!)**
  - **Resistance is increased in biofilm state**

MICRBOIAL LIFE FORMS CYCLE



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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!!!

BIOFILM – A SELECTIVE ENVIRONMENT

- **Biofilms are selective – certain surfaces inhibit certain organisms**
  - **Pseudomonas will not stick to copper pipe**
- **Copper pipe has to be "primed" by presence of certain proteins or other organisms**
- **M.avium is a "biofilm pioneer" (Falkinham)**
- **The fatty membrane, or hydrophobic membrane drives adherence to to surfaces *of all compositions***

BIOFILM AND NTM

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

MYCOBACTERIAL OUTER MEMBRANE

- **The major determinant of M. avium complex ecology is the lipid and wax-rich outer membrane that surrounds the cell**
- **Long-chain fatty acids (C60-80) that make up 30% of the entire cell mass**
- **This membrane is responsible for slow growth (1 gen/day)**
- **Substantial amount of energy/ fuel is diverted to production of the fatty membrane**
- **This creates hydrophobic nature to the organism; a droplet of water forms a bead on the surface of M. avium cells**
- **The outer membrane is impermeable to to nutrients – *clearly a down side***
- **The outer membrane is at the same time resistant to disinfectants (chlorine) and other metals that are microbe toxic – *an advantage!!***

NTM HABITATS

- NATURAL WATERS
- DRINKING WATER
- HOUSEHOLDS
- AEROSOLS
  - Shower heads and water taps
- WATER FILTERS
- ROOM HUMIDIFIERS
- BIOFILM FEATURE KEY IN HUMAN WATER

- SOILS
- DUSTS

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 IN THE KITCHEN

- **NTM isolated kitchen sink biofilm, household refrigerator taps and home ice makers**
- **NTM has been isolated from certain foods and may be involved in the association between swallowing disorders and esophageal dysfunction (GERD and LPR)**

BIOFILM IN NTM DISEASE

- NTM LD (lung disease) often occurs in patients with underlying disease (old TB, silicosis, bullous disease, lung cavities
- NTM form biofilm in the cavities and progress to cause disease

- This is more recently recognized in 1980's-90 re Lady Windermere Syndrome, including chronic bronchiectasis and Cystic fibrosis

- ***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

- Biofilm critical in catheter, dialysis infection and recent M. chimera infections in bypass surgery patients

PERSONAL ENVIRONMENT
ENVIRONMENTAL MYCOBACTERIAL LATENCY

Schraufnagel, 2017

- **Reviewed study above of Ford noting that most patients ran into clinical trouble based on co-morbidities rather than NTM**
- **Studied country of origin of patients:**
  - **M. fortuitum increased in Asian-born**
  - **M. lentiflavum increased in African-born**
- **Pathology specimens indicate that NTM reside in sub-epithelia of small airways of bronchiectatic airways and biofilms**

THUS: Is it possible that individuals harbor organisms far longer than we think AND that they cause bronchiectasis?

NTM: IMPORTANCE OF BETTER PREVENTION

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

Worthwhile identifying *source* of infection

CONCLUSIONS FOR NOW

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

Uncertain which individual exposure(s) and behaviors are involved

CONTROL OF NON-TUBERCULOUS INFECTION PROPOSED CONCLUSIONS

- **Mycobacterial transmission routes proceed from natural reserves to households via WDS's**
- **Global spread of pulmonary MAC disease may be caused by human activities as individuals carry organisms on their belongings**
- **Need to create living environments more comfortable to individuals and less comfortable to NTM organisms**
- **Need to disrupt biofilms**
  - **In water systems**
  - **In airways**

THANK YOU FOR YOUR ATTENTION