



NON-TUBERCULOUS MYCOBACTERIAL INFECTION

EPIDEMIOLOGY & EVALUATION

**Pulmonary disease
Non-HIV Population**

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NOVEMBER 2017

GOALS OF TALK

Epidemiology: The branch of medicine that deals with the incidence, distribution, and possible control of diseases

- **Updates re epidemiology of the disease**
- *Many of you know much of this, but...*
- **Understand why epidemiology is important in understanding *the disease***
- **Understand why epidemiology is important in evaluating *the individual patient***

- **Gain perspective on how the *host factors* are the pivotal factors in acquiring the infection**

EVALUATION

- Outline current evaluation *algorithm*
 - Often *multifactorial*
 - Emphasize importance of *systematic* evaluation
- Evaluate the *organism*
- Evaluate the *patient*
- Implications of findings
- Implications for management

As always, a lot to cover!

EPIDEMIOLOGY: PREVALENCE DATA

- Adjemian, Olivier, Seitz, Holland, Prevots, NIH. 2012
- Purpose: Assess prevalence of PNTM
- Medicare claims 1997-2007 – 5%
- Age 65+
- Annual prevalence rose from 20/100,000 to 47/ 100,000
- 8.2% per year increase
- Women 1.4 more likely than men to be PNTM case than men

PREVALENCE: POPULATION-BASED

Henkle, Winthrop, et al. 2015

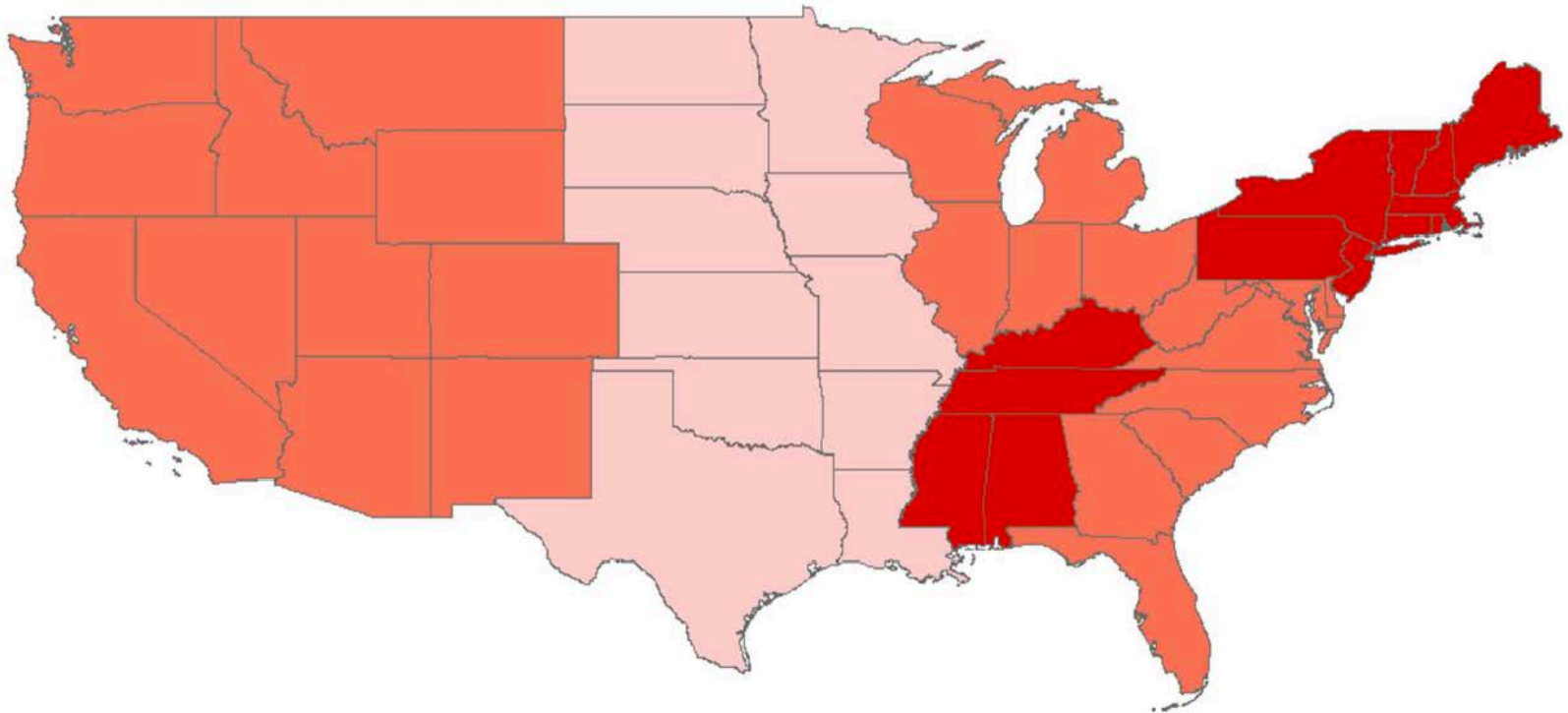
- Contacted all labs in Oregon performing mycobacterial cultures on *all-age* Oregon residents
- 2007-2012
- Defined “cases” of PNTM “**disease**” as those meeting ATS criteria of 2 or more positive cultures or one BAL specimen (more precise)
- Median age was 69 years (0.9-97)
- Female to male 56:44
- Under age 60 more likely male
- Incidence increased with age
- Prevalence increased *slightly* over interval (not significant)
- MAC 86%. M.abscessus/ chelonae 6%

PREVALENCE: FIVE STATES 2008-2013

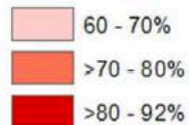
Donohue et al. 2-16

- Studied distribution of patients with at least **ONE** positive culture
- 2008-2013
- Maryland, Mississippi, Maryland, Wisconsin, Ohio
- Prevalence rose **8.7 to 13.9** per 100,000 over that five year period
- **Mississippi:** Cases greatest ages **80+**
- **Wisconsin:** Cases greatest ages **60-69**

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



Proportion of NTM isolates identified as MAC



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**
- *****Probable significant under-coding of disease based in ICD-9 coding**

EPIDEMIOLOGY: 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?

EPIDEMIOLOGY: COURSE OF DISEASE

Winthrop, et al. 2017

- Followed 369 patients with respiratory NTM isolates 2005-2006
- 84% MAC
- 35.1% died within 5 years
- *Slight increase in those meeting ATS criteria (> 2 positive cultures): 28.7 vs. 23.4*
- Conclusions:
 - *Number of positive cultures does not correlate with outcome, i.e. “cases” do not do worse than non-cases*
 - **Most patients died from causes other than NTM**

OUTCOMES: RISK FACTORS AND SPECIES

Ford, et al. 2017

- Washington State NTM cultures 1998-2011 examined
- Bronchiectasis most common co-morbidity for NTM isolation
- 72% of 168 followed had one major co-morbidity
- 56 patients met ATS criteria for treatment; 22 treated; 19% abscessus and kansasii
- ***Mortality rate most often from *co-morbidities* rather than from NTM

IMPORTANT IMPLICATION

**If you take care of your overall health,
you are likely to do fine!**

EPIDEMIOLOGY: LONG-TERM OUTCOMES

Henkle, Winthrop, et al. 2017

- Reviewed in 2014-2015 patients with one or more isolates 2005-2006
- 172 patients studied. *M. avium* 89% cases and 74% non cases
- 59% had multiple pos. isolates; 4% non-cases became cases
- *54% cases and 9% of baseline non-cases were treated*
- *Of those alive at 10 years,*
 - *89% had persistence of positive CT findings*
 - *49% had persistence of positive cultures*

Conclusion: It is usually a long-term infection

EPIDEMIOLOGY II

SOURCE OF THE ORGANISM

OPPP'S

Opportunistic premise plumbing pathogens

- NTM are **saprophytic organisms**
 - Grow within ***engineered*** water systems
 - Less well understood
 - Not human-to-human spread

BIOFILM

- **The slimy film that coats all (non-copper) pipes**
- **All water mains, pipes leading to the home and in the home have them**

- **All but impossible to eliminate**

BTW: Plastic rather than copper pipes proposed as a reason for uptick in NTM from showers, etc.

BIOFILM AND NTM

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

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”

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

- Perhaps a new in-between level of water exposure:
- *Not* the ambient climate and *not* the pipes in your house

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**

EPIDEMIOLOGY CONCLUSIONS

- **Mycobacteria are from water – biofilm**
- **Ambient water and home water are both factors**
 - **Hawaii and Louisiana – “atmospheric”**
 - **Plumbing – “in your four walls”**
 - ******Living near a stream – new level of concern**
- **There is no true “safe haven from NTM; you just change the relative risk of which organism**
- **The host factors seem to prevail**
- **Play your cards right re overall health and you’ll do OK re NTM!**

EVALUATION

EVALUATION: THE ORGANISM

- **Source of the isolate**
 - Sputum
 - Induced sputum
 - Bronchoscopy
- **How many isolates?**
- **How many organisms?**
- **What are our expected findings? Per geography**
 - *M.simiae*
- **What other organisms are isolated? Pseudomonas? Aspergillus?**

EVALUATION: THE ORGANISM

- **M. avium**
 - **Count on macrolide sensitivity (clarithromycin/ azithromycin)**
 - **Test clarithro as same class as azithromycin**
 - **Other antibiotic (e.g. ethambutol, rifamycins) tests far less reliable**
 - **Commercial labs less reliable**
 - **Amikacin can be tested**
 - **Ethambutol used “anyway”**
- **When to request sensitivity?**
 - **Repeat treatment**
 - **Treatment “failure”**
 - **Too slow to convert sputum**
 - **Patient worse**

EVALUATION: THE ORGANISM

- Rapid growers(RGM):
- Separate *M. abscessus* from *chelonae* and *fortuitum*
- Further identify *abscessus*
- **Inducible** resistance
 - Erythromycin ribosomal methylase gene, *erm(41)* modifies the binding site for macrolides **resulting in resistance in presence of macrolide**
 - Functional gene present in most *M. abscessus* subspecies *abscessus* and *bolletii*
 - *M. abscessus massiliense* *does not possess this gene*

EVALUATION: THE ENVIRONMENT

- Water and soil organism
- Agriculture workers
- Hot tubs
- (Steam rooms, room humidifiers, others??)

- Problem: It is in *everyone's* home
 - Husband and wife
 - Apartment and pool health club
 - Different *M. avium* subtypes and home sources!!

- Geography
 - Regional – Hawaii, Louisiana vs. desert states
 - Proximity to water

EVALUATION: THE PATIENT

**HOST FACTORS LIKELY
OUTWEIGH
ALL OTHERS**

EVALUATION: THE PATIENT

- Anatomic predisposition
 - Bronchiectasis
 - Location and extent
 - COPD
 - Interstitial lung disease
 - Other lung damage
 - Sarcoidosis
- Immune deficiency
 - Immunoglobulin deficiency
 - Alpha-1-antitrypsin def
 - Cystic fibrosis (younger patients) – subclinical types – sweat test/blood
 - Ciliary dysfunction
 - *Most other genetic abnormalities not clinically relevant*

EVALUATION: THE PATIENT

- Recent additions:
- Swallow dysfunction (Dr. Balou) - *routine*
- Esophageal dysfunction (Dr. Khan) - *routine*
- Vocal cord dysfunction (Dr. Amin) – *per above*

We are particularly fortunate to have these specialists involved

EVALUATION: THE PATIENT

- **Immune compromise: External factors**
- **Medications:**
- **Immune modifying**
- **Need to be specific**
 - **Prednisone/ systemic steroids-**
 - **Relative**
 - **How much?**
 - **For how long?**
 - **Biologics/ TNF alpha inhibitors**
 - **Inhaled/ topical steroids**
 - **New to the list**
 - **Relative as well**

CONCLUSIONS FOR NOVEMBER 2017

TWO HIT/ MULTI HIT HYPOTHESIS

- **Environmental**
 - Organism virulence
 - Organism exposure burden

- **Genetic**
 - Single gene
 - Polygenic
 - *Other* intrinsic factors



THANK YOU FOR YOUR ATTENTION