Epidemiology of Nontuberculous Mycobacterial Pulmonary Disease

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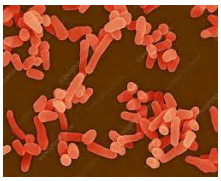
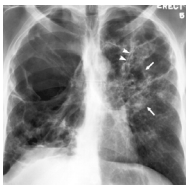
Disclosure

- No relevant financial relationships.

Nontuberculous Mycobacterial Lung Disease

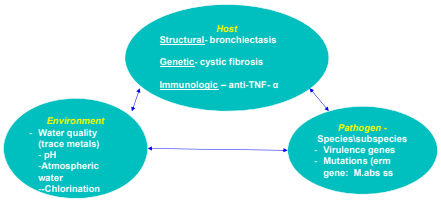




Overview

- Review pathogen features
- Discuss host risk factors
- Interface of host and environment
  - Individual risk factors
  - Ecologic risk factors

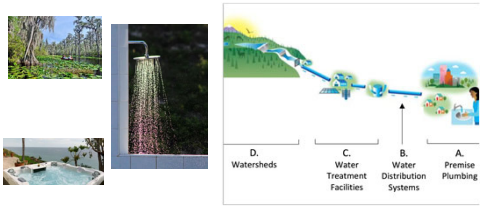
NTM Risk: Host-Environment-Pathogen



Quiz: What are environmental sources of NTM? (check all that apply)

a) Aerosols
b) Dust
c) Refrigerator ice maker
d) Hot tubs
e) Potting soil
f) Zebrafish
g) Okefenokee swamp

Nontuberculous Mycobacteria: Multiple Sources of Environmental Exposure



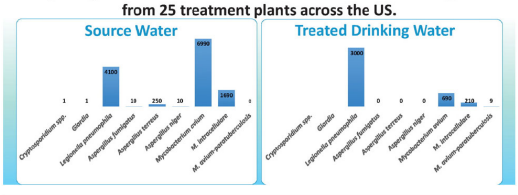
Nontuberculous Mycobacteria Concentrate in Municipal Water Systems

- Mycobacteria have lipid-rich mycolic acid outer membrane
  - Hydrophobic
  - Resistant to disinfection (chlorine, chloramine)
  - Form biofilms on plumbing surfaces
  - Favor acidic pH,
  - Relatively heat resistant
  - Growth stimulated by humic and fulvic acids (brown water swamps)
  - Grow best around 25- 37 C (varies by species)
- >180 species: some species variation in ecologic niche
  - MAC (avium and intracellular)- around 80% in US
  - M. abscessus, around 15%, more common in the Southeast

Microbial pathogens in source and treated waters from drinking water treatment plants in the United States and implications for human health

Dawn N. King [a,1], Maura J. Donohue [a,1], Stephen J. Vesper [a,1], Eric N. Villegas [a,1], Michael W. Ware [a,1], Megan E. Vogel [b], Edward F. Furlong [c], Dana W. Kolpin [d], Susan T. Glassmeyer [a], Stacy Pfaller [a,e,1]

Nine pathogens measured in source waters and treated drinking waters from 25 treatment plants across the US.



M avium and M intracellulare
- **25% of source**
- **36% of treated**

Science of the Total Environment 562 (2016) 987–995

HOST FACTORS

Risk Factors for PNTM: Host Factors

Host Factor	RR, OR, or Relative Prevalence
Lung Cancer	3.4
COPD	2-10
Bronchiectasis	44, 187.5
Thoracic skeletal abnormalities	5.4
Low body weight	9.1
Rheumatoid arthritis	1.5 ,1.9
Immunomodulatory drugs/anti-TNF agents	2.2/1.6-2.9
Steroid use	1.6, 8
Gastroesophageal reflux disease	1.5, 5.3
Cystic Fibrosis	

Review. Clinics in Chest Medicine; 2015; 36:13-34

In a US population sample (4 HMOs), most common underlying conditions are COPD, Bronchiectasis, and Malignancies- no one condition is present for all, and many are idiopathic

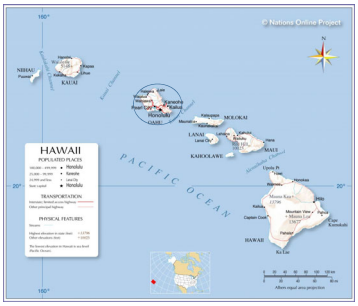
TABLE 5. ASSOCIATED CONDITIONS AND SYMPTOMS CODED DURING THE 3 MONTHS BEFORE OR 6 MONTHS AFTER DETECTION OF A POSITIVE SPECIMEN, POSSIBLE AND DEFINITE CASES, THREE INTEGRATED HEALTH CARE DELIVERY SYSTEMS

Diagnosis or Symptom (*ICD9 code*)	Possible Cases	Definite Cases
Pulmonary nontuberculous mycobacteria (031.0)	638 (16)	488 (26.9)
Bronchiectasis (494, 494.0, 494.1)	628 (16)	427 (23.6)
Chronic obstructive pulmonary disease (496, 491)	1,256 (32.3)	511 (28.2)
Pneumonia, unspec (486)	1,224 (31.4)	603 (33.3)
Asthma (493.2, 493.9)	446 (11.5)	223 (12.3)
Other lung disease not elsewhere classified (518.89)	419 (10.8)	249 (13.7)
Malignancies (140-239, excluding 173)	838 (21.5)	454 (25)
Congestive heart failure (428.0)	422 (10.8)	188 (10.4)
Gastroesophageal reflux (530.81)	388 (10.8)	207 (11.4)
Cough (786.2)	916 (23.5)	508 (28)
Shortness of breath (786.05)	401 (10.3)	215 (11.9)
Hemoptysis (786.3)	443 (11.4)	264 (14.6)
Total	3,894	1,812

Prevots, Shaw, Strickland, *et al.*: NTM Prevalence

Am J Respir Crit Care Med Vol 182. pp 970-976. 2010

The State of Hawaii: 8 Main Islands



BMI and Ethnic Differences in NTM PD Incidence, Hawaii

- Collaboration with Kaiser Permanente Hawaii
- n=505,202 beneficiaries, Kaiser Permanente Hawaii
- Population: 28 different ethnic categories
  - 48% “any” Asian
    - 20% Filipino
    - 13% Japanese
    - 7% Chinese
  - 26% “any” Native Hawaiian \ Pacific Islander
  - 44% “any” White

Host Genetics and NTM PD Susceptibility: NTM a Multigenic Disease: GWAS, Whole Exome, Candidate Gene Approaches

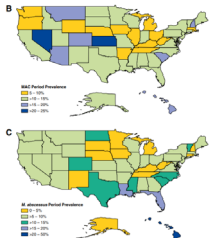
- GWAS SNP associated with CHP2 lung protein, in Korean and European patients with nodular bronchiectatic subtype (1)
- Whole exome sequencing: candidate gene TTK and 6q12-q16 Linkage Region (2)
- Whole exome sequencing, candidate gene analysis:
  - NTM PD patients have significantly more variants in immune, CFTR, cilia, and connective tissue categories (3)

- 1- European Respiratory Journal 2021 58: 19022692
- 2- Am J Resp CC Med 2017; 196: 1599-1604
- 3- Am J Resp Crit Care Med 2015; 192: 618-28

Quiz: Which State in the US has the highest prevalence of NTM-PD?

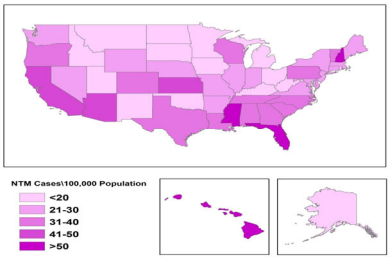
A. Rhode Island
B. Florida
C. Montana
D. Hawai'i
E. Colorado

Geographic Variation in NTM Prevalence Among Persons with Cystic Fibrosis: M. Abscessus Prevalence Highest in the Southeast United States



Tzou, Dirac, Becker, et al.: NTM Exposure and Pulmonary Disease AnnalsATS Volume 17 Number 1 | January 2020

Highest Prevalence of Nontuberculous Mycobacterial Pulmonary Disease in Hawai'i and Florida, 2010



From Strollo et al: the burden of pulmonary NTM in the United States. Annals ATS 12; 2015: 1458-1464

cases per state: 1208, range 48-12,544
2010 estimated USA total: 86,244 cases, cost of $815 million

How do people become infected with NTM?

- Water
  - GERD (aspiration)
  - Aerosols
- Soil aerosols
  - Peat moss
  - Gardening
- Environmental sampling has identified NTM in outdoor and indoor (shower) aerosols
- Multiple studies showing genetic matches between clinical isolates and samples taken from soil and household plumbing
- Risk will depend on local ecology as well as individual behaviors

Epidemiologic Studies: Associating Disease or Infection Risk with Individual Behaviors and Environmental Factors

Risk Factors for PNTM: Environmental-individual Exposures

Individual environmental exposure	RR, OR, or Relative Prevalence
Indoor swimming pool use (in past 4 months), persons with Cystic Fibrosis (US, 2014)	5.9 (1.3, 26.1)
Soil exposure, non-CF (Japan 2011)	5.9 (1.4, 24.7)
Shower MAC abundance (Oregon; 2020)	4.0 (1.2, 13.4)
Public baths >1 week (Japan; 2021)	2.8 (1.6, 5.2)

Adapted from: Pulmonary Infection with Nontuberculous Mycobacteria review. Clinics in Chest Medicine; 2015; 36:13-34

Shower Aerosols significantly Associated with MAC Pulmonary Disease, Case-Control Study, Oregon

Table 1. Association of residential nontuberculous mycobacteria and *M. avium* complex pulmonary disease by point-of-use source

Household site	*N* (Positive)*		Unadjusted Analysis		Age-adjusted Analysis†		Fully Adjusted Analysis‡	
	Cases	Control Subjects	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
Bathroom faucet	40 (23)	48 (20)	1.7	0.8–4.0	1.8	0.7–4.3	2.1	0.8–5.5
Kitchen faucet	40 (23)	48 (22)	1.6	0.7–4.0	1.4	0.6–3.5	1.6	0.6–4.2
Shower aerosols	39 (18)	46 (10)	3.2	1.1–8.9	3.8	1.2–11.7	4.0	1.2–13.4
Indoor soil	30 (17)	38 (13)	2.0	0.7–5.4	1.6	0.6–4.6	1.4	0.5–4.4
Outdoor soil	39 (10)	46 (9)	1.2	0.4–3.4	1.1	0.4–3.2	1.2	0.4–3.4

Table 2. Association of residential *M. avium* complex and *M. avium* complex pulmonary disease by point-of-use source

Household site	*N* (Positive)*		Unadjusted Analysis		Age-adjusted Analysis†		Fully Adjusted Analysis‡	
	Cases	Control Subjects	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
Bathroom faucet	40 (15)	48 (11)	1.8	0.7–4.5	1.7	0.6–4.5	1.8	0.6–4.9
Kitchen faucet	40 (15)	48 (14)	1.2	0.5–2.6	1.1	0.5–2.5	1.2	0.5–2.8
Shower aerosols	39 (10)	46 (6)	2.6	0.7–10.4	2.9	0.7–12.5	2.9	0.7–12.4
Indoor soil	30 (7)	38 (4)	1.9	0.5–6.4	1.3	0.3–5.0	1.1	0.3–4.5
Outdoor soil	39 (8)	46 (8)	1.0	0.3–3.1	0.9	0.3–2.8	0.9	0.3–2.8

Tzou, Dirac, Becker, *et al.*: NTM Exposure and Pulmonary Disease AnnalsATS Volume 17 Number 1 | January 2020

In South Korea, frequent use of public baths associated with increased risk of M. avium-associated disease (case-control study)

Table 4. Comparison of Water Exposure between the Two Groups

	NTM-PD* (n=102)	Control (n=217)	*p* value	OR† (95% CI)
Shower, ≥1 time/day	56 (54.9)	130 (59.9)	0.469	0.96 (0.57–1.64)
Public bath	63 (61.8)	119 (54.8)	0.296	1.76 (1.04–3.04)
≥1 time/week	36 (35.3)	42 (19.4)	0.003	2.84 (1.58–5.17)
Hot tub	46 (45.1)	65 (30.2)	0.278	1.69 (0.99–2.91)
≥1 time/week	24 (23.5)	35 (16.1)	0.152	2.17 (1.13–4.17)
Wet sauna	41 (40.2)	73 (33.6)	0.310	1.76 (1.02–3.05)
≥1 time/week	15 (14.7)	24 (11.1)	0.457	1.89 (0.87–4.04)
Swimming	9 (8.8)	17 (7.8)	0.935	1.59 (0.61–3.93)
≥1 time/week	8 (7.8)	11 (5.1)	0.470	2.27 (0.79–6.34)
Duration, yr	8.1±7.5	16.7±18.0	0.097	
Dishwashing	90 (88.2)	185 (85.3)	0.585	1.05 (0.40–2.82)
≥1 time/day	80 (88.9)	164 (88.6)	>0.999	0.67 (0.21–2.11)
Humidifier at home	17 (16.7)	31 (14.3)	0.699	1.16 (0.57–2.29)
≥1 time/week	15 (14.7)	24 (11.1)	0.457	1.34 (0.63–2.80)

CI, confidence interval; NTM-PD, nontuberculous mycobacterial pulmonary disease; OR odds ratio.
Data are presented as numbers (%) or means±standard deviation.
*NTM-PD patients with *M. intracellulare* infection were excluded, †Adjusted for age, sex, body mass index, smoking, history of tuberculosis, and history of

The Association between Behavioral Risk Factors and Nontuberculous Mycobacterial Pulmonary Disease — Yonsei Med J 2021 Aug;62(8):702-707

Quiz: What defines an ecologic study?

A. You look at trees

B. Exposure is measured at the population level (environmental factors by geographic area of residence), not at the individual level

C. You go fishing and test the fish for *M. marinum*

D. You catch birds and test for *M. avium*

E. None of the above

Environmental factors associated with infection and disease

Environmental: climatic and population factors		
Proportion of area as surface water	4.6[17]	Disease
Mean daily potential evapotranspiration	4.0[17]	Disease
Copper soil levels, per 1 ppm increase	1.2 (1.0, 1.2)[17]	Disease
Sodium soil levels, per 0.1 ppm increase	1.9 (1.2, 2.9)[17]	Disease
Manganese soil levels, per 100 ppm increase	0.7 (0.4, 1.0)[17]	Disease
Increased average topsoil depth	0.87 (*Mycobacterium intracellulare*)[18]	Disease
Soil bulk density	1.8 (*Mycobacterium kansasii*)[18]	Disease

Prevots DR and Marras T. Epidemiology of human pulmonary infection with nontuberculous mycobacteria: a review. Clin Chest Med 2015; 36: 13-34

Ecologic studies: Exposures measured at population level, not individual level

Nontuberculous Mycobacterial Disease and Molybdenum in Colorado Watersheds

Ettie M. Lipner [1,2,*], Joshua French [3], Carleton R. Bern [4], Katherine Walton-Day [4], David Knox [5], Michael Strong [1], D. Rebecca Prevots [6,†] and James L. Crooks [1,2,†]

Nontuberculous mycobacterial infection and environmental molybdenum in persons with cystic fibrosis: a case–control study in Colorado

Ettie M. Lipner[1,2✉], James L. Crooks[2,3], Joshua French[4], Michael Strong[1], Jerry A. Nick[5,7] and D. Rebecca Prevots[6,7]

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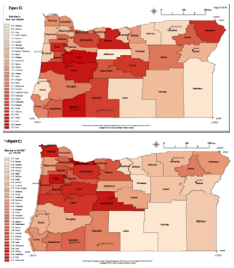
NTM Infection Risk and Trace Metals in Surface Water: A Population-Based Ecologic Epidemiologic Study in Oregon, 2007-2012

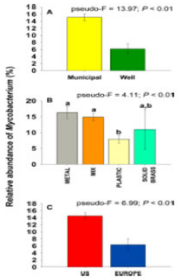
- Water quality data from EPA\USGS associated with statewide laboratory-based NTM surveillance data, using patient county of residence
- For every 1-unit increase in the log concentration of vanadium in surface water, the risk of MAC increased by 49%
- For every 1-unit increase in the log concentration of molybdenum, the risk of M. abscessus infection increased by 41%
- These trace metals may be important in mycobacterial metabolism



Ann Am Thorac Soc . 2021 Sep 28. doi: 10.1513/AnnalsATS.202101-053OC. Online ahead of print.

Differences in the Relative Abundances of Mycobacteria (via 16S rRNA gene sequencing) Across Households in the United States, 2016

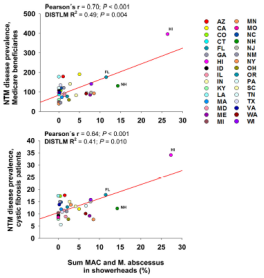
Showerhead film samples collected from 656 households in US and Europe (n=50) by "citizen scientists"
-16sRNA used to identify mycobacteria (direct, non culture)
- Mycobacterial abundance greater in:
- Municipal water vs. well water
- Plastic pipes vs. metal
- US showerheads than in Europe



Gebert et al. Ecologic Analysis of Mycobacteria in Showerhead Biofilms and Their Relevance to Human health Ecologic and evolutionary science 2018; 9

Relationship Between Relative Abundance of MAC and M. abscessus in Showerheads and NTM Disease

Prevalence of NTM-PD was significantly correlated with disease among both
- Medicare beneficiaries and persons with CF
- HI, FL, southern CA, mid-Atlantic: highest prevalence and also highest mycobacterial abundance



Gebert et al 2018; mbio 9; e01614

TRENDS

NTM PD Incidence Increasing by 5.2% per Year, 2008-2015 (Optum EHR database- 74 million beneficiaries)

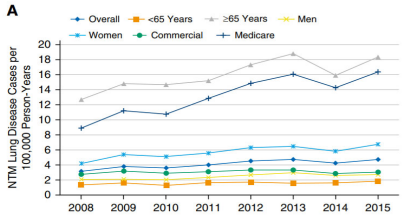


Figure 2. (*A*) Yearly incidence and (*B*) yearly prevalence of nontuberculous m national health insurance plan.

Incidence and Prevalence of Nontuberculous Mycobacterial Lung Disease in a Large U.S. Managed Care Health Plan, 2008–2015

Ann Am Thorac Soc Vol 17, No 2, pp 178–185, Feb 2020

AFB testing increased 3.2%/year and NTM positivity increased 4.5%/year, 2009-2015 (Cerner EHR database, 31 facilities)

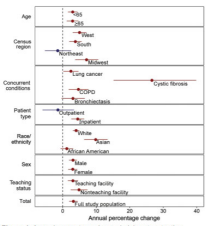


Figure 1. Annual percentage change in laboratory testing for acid-fast bacilli in 31 facilities, United States, 2009–2015

Mycobacterial Testing Trends, United States, 2009–2015[1]

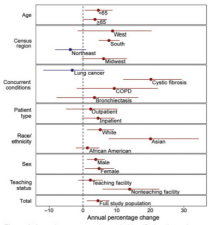


Figure 2. Annual percentage change in identified pathogenic nontuberculous mycobacteria (NTM) in 31 facilities, United States, 2009–2015. Red indicates increasing trends; blue indicates

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 26, No. 9, September 2020

Annual Prevalence of Pulmonary NTM, North America, Japan, Korea

Geographic area	Disease definition	Annual isolation rate/ 100,000	Annual disease rate/ 100,000
Hawaii (Kaiser)	Microbiologic	44 (2013)	
US- Pacific Islands (2011)	Microbiologic	48 (2011)	
5 States (MO, MS, MD, OH, WI), NTM reporting	Microbiologic	8.7-13.9	n/a
North Carolina, 3 counties (2006-2010)	Microbiologic	9.4	
Oregon USA (2007-2012)	Microbiologic	12.7	5.9
USA: HMOs (CA, CO, PA, WA) (1997-2005)	Microbiologic	11.8	5.5
Ontario, Canada (1998-2010)	Microbiologic	22.2	9.8
S Korea (2009-2016)	ICD9	n/a	36.1 (2016)
Japan 2012	Micro, clinical, ICD9		24 (2012/3) 29 (2011)

Prevots DR, Marras TK. Epidemiology of Human Pulmonary Infection with Nontuberculous Mycobacteria: a review. Clinics in Chest Medicine; 2015; 36:13-34

Annual Prevalence of Pulmonary NTM, Europe

	Disease definition	Annual isolation rate per 100,000	Annual disease rate
England, Wales, Northern Ireland (2007-2012)	Micro	7.6 (2012)	n/a
Scotland (1992-2010)	Micro, clinical	NR	3.1 (2005-2010)
Leeds, UK (1995-1999)	Micro, clinical	2.9	1.7
Denmark (1997-2008)	Micro, clinical	2.5	1.1
Netherlands (1999-2005)	Micro , clinical	6.3	2.3-4.5 (2012-2019)
France (2001-2003)	Micro, clinical	NR	0.73
Central Greece (2004-2006)	Micro, clinical	7.0	0.7

Summary

- Geographic variation in NTM-PD explained by environmental factors: water, soil
- NTM PD results from susceptible host in high exposure environment
  - Mycobacterial abundance in showerheads correlated with disease prevalence
  - Abundance also correlated with chlorine, pH, alkalinity
    - Chlorine concentration 11x higher in U.S. municipal water vs. Europe municipal shower water
  - Mutiple potential exposures
  - Household plumbing a common exposure
  - Attributable exposures will depend on the population

Thank you