Host Risk Factors for Non-tuberculous Mycobacterial (NTM) Infections

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Thank you to the organizers, colleagues, and patients, from whom I continue to learn!

No conflicts of interest

NTM Lecture Series for Providers
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OUTLINE

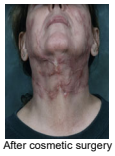
- **D**iseases caused by NTM reflects underlying risk factors.
- **R**isk factors for skin, soft tissue, and traumatic orthopedic infections.
- **R**isk factors for disseminated disease.
- **R**isk factors for isolated lung disease.
- **W**hat predisposes to NTM lung disease without classic risk factors?

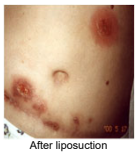
Diseases caused by NTM reflects underlying risk factors

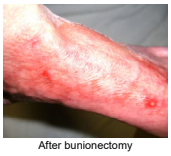
- **Skin, soft tissue, & traumatic orthopedic infections** ← "accidental or iatrogenic + *locus minoris resistentiae*"
- **Isolated lung disease** ← "structural lung disease"
- **Extrapulmonary visceral and disseminated infections** ← "some underlying significant immunodeficiency"

Risk factors for skin, soft tissue, and traumatic orthopedic NTM infections

- **Breach of skin** – accidental trauma, foot salons, medical procedures with contaminated water, instrument, or medications.
- Most cases occur in those with normal host immunity…but we contend that physical trauma itself may be predisposing.

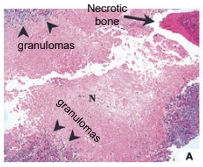

After cosmetic surgery


After liposuction

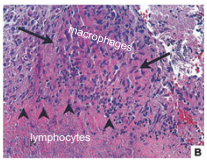

After bunionectomy

Why did this healthy teenager get a localized NTM infection of the spine?

- A 16 y.o. girl suffered multiple falls from competitive roller skating, resulting in abrasions, MSK pains, and recalcitrant backache.
- MRI revealed an enhancing signal in T9 with anterior paraspinal soft tissue mass from T8-T10.
- Biopsy of T9 revealed necrotizing granulomas and culture was +ve for *M. abscessus*.



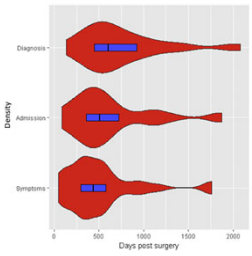
T9 vertebra biopsy



Higher power of granuloma

M. chimaera and open-chest heart surgery

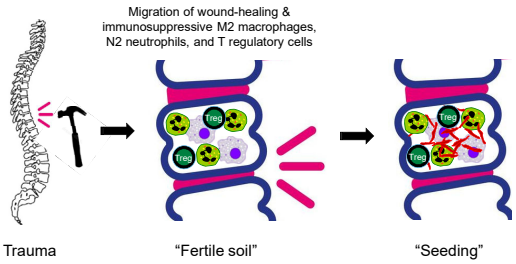
- Beginning in 2013, *M. chimaera* infections were reported of patients who underwent open-chest heart surgery.
- Infections involved the **hardware**, **surgical wounds**, and **disseminated disease**.
- *M. chimaera* traced to **contaminated heater-cooler units** (“heart-lung machine”) and the bioaerosols generated.



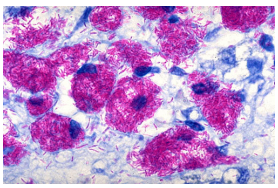
Scriven JE et al. Clin Microbiol Infect 2018

We hypothesized that the site of trauma is "fertile soil" for seeding of infection

"locus minoris resistentiae"

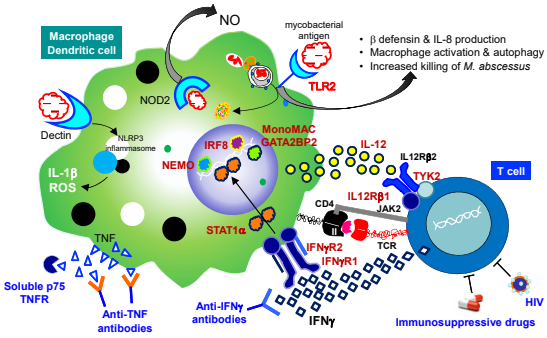


Risk factors for disseminated NTM disease



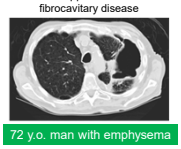
Dupont isolator

Genetic & acquired causes of disseminated NTM disease

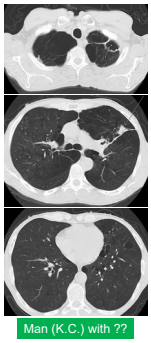


Structural lung disease is a major risk factor for isolated NTM-LD (excluding HP)

Upper lobe fibrocavitary disease

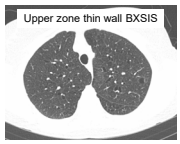


72 y.o. man with emphysema

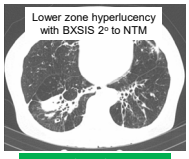


Man (K.C.) with ??

Upper zone thin wall BXSIS

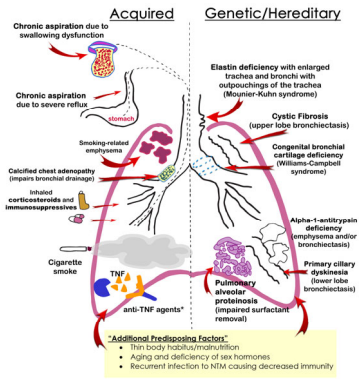


Lower zone hyperlucency with BXSIS 2° to NTM



Woman (M.M.) with PiZZ genotype of AAT

Risk factors for isolated NTM-LD



Other genetic disorders associated with NTM-LD:

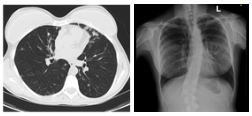
- Fibrillin-2
- MICA
- NRAMP1
- MST1R
- TLR2
- VDR

What predisposes to NTM lung disease without classic risk factors?

Women and men with NTM-LD without obvious risk factors not uncommonly have a unique body morphotype

- **Slender body habitus, scoliosis, pectus excavatum**. This phenotype is often referred to as the Lady Windermere syndrome.

41 year-old previously healthy woman life-long slender body habitus, severe scoliosis, and NTM lung disease



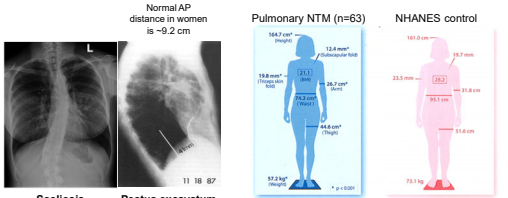
- Reich and Johnson described 29 patients (all women with no obvious risk factors) with NTM-LD, localized mostly in the RML and lingula. They hypothesized that because women generally don't expectorate their phlegm (in public), this predisposes them to NTM infections (Chest 1992).
- Lord Windermere syndrome – similar characteristics between men and women with NTM-LD (Holt M et al. Eur Respir J 2019).

Analyses of Lady W phenotype and NTM-LD

1. How strong is the link between Lady W phenotype and NTM-LD?
2. Could slender body habitus ***itself*** be a risk factor for NTM-LD?
3. Is there a genetic basis for NTM-LD patients with the Lady W phenotype?

1. How strong is the link between Lady W phenotype and NTM-LD?

NTM-LD patients are often taller and skinnier with thoracic cage abnormalities



Scoliosis
MAC (52%)
M. tb (13%)
Gen. pop (1%)

Pectus excavatum
MAC (27%)
M. tb (9%)
Gen. pop (2.5%)

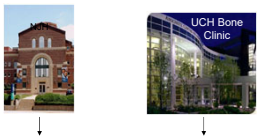
Scoliosis (51%)
Pectus excavatum (11%)
MVP (9%)

Self-reported BMI before pNTM = 22.3
Disseminated NTM (n=8) (BMI) = 26.4

Kim RD et al. AJRCCM 2008

Iseman MD et al. ARRD 1991

Experimental Design



103 NTM-LD patients enrolled

101 controls enrolled

Demographics
Height, BMI, and % body fat by anthropometric measurements
Scoliosis and pectus excavatum
Blood leptin levels
Blood levels of cytokines

Exclusionary Criteria:
- Active cancer
- Currently on immunosuppressive agents
- History of NTM infection (for the control group)

Patients with Nontuberculous Mycobacterial Lung Disease Exhibit Unique Body and Immune Phenotypes

Marinka Kartalija[1], Alida R. Ovrutsky[2], Courtney L. Bryan[1,3], Gregory B. Pott[1,3], Giamila Fantuzzi[4], Jacob Thomas[5], Matthew J. Strand[5,6], Xiyuan Bai[2,7], Preveen Ramamoorthy[2], Micol S. Rothman[8], Vijaya Nagabhushanam[2], Michael McDermott[8], Adrah R. Levin[2], Ashley Frazer-Abel[9], Patricia C. Giclas[9], Judith Korner[10], Michael D. Iseman[1,2,7], Leland Shapiro[1,3], and Edward D. Chan[2,3,7]

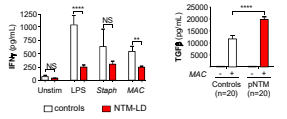
AJRCCM 2012

pNTM patients are taller, skinnier, and have greater prevalence of scoliosis & PEX

	NTM-LD (n=103)	Controls (n=101)	p-value
Age (yrs ± SD)	64 ± 11	61 ± 16	0.11
Female gender	83%	89%	0.18
Caucasian	90%	87%	0.49

Variable	NTM-LD (n=103)	Controls (n=101)	p-value
Height (cm)	166.94 ± 7.62	161.83 ± 8.40	<0.0001
BMI (kg/m^2)	22.06 ± 3.81	23.98 ± 5.07	0.003
Body fat (%)	28.46% ± 7.42	31.28% ± 7.60	0.008
Scoliosis	31%	13%	0.0006
Pectus excavatum	87%	65%	0.01

Whole blood of pNTM patients produce less IFNγ and more TGFβ

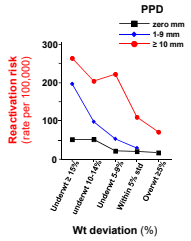


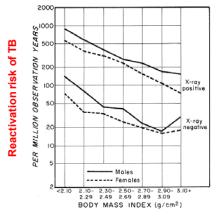
No difference in IL-1β, IL-6, IL-8, RANTES, IL-12, IL-18, TNFα

2. Could slender body habitus *itself* be a risk factor for NTM-LD?

68,754 U.S. Navy Recruits (1949-1951)
Palmer CE et al. *Am Rev Tuberc* 1957

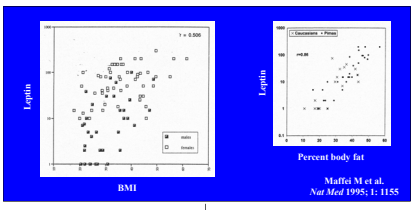
1,717,655 Norwegiens with compulsory miniature X-rays (1963-1975)
Tverdal A. *Eur J Respir Dis* 1986





Q: Why are thin individuals more susceptible?

Hypothesis: due to a relative deficiency of leptin

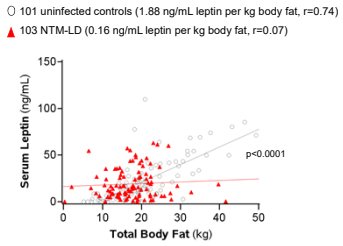


Thus, in humans, the more fat, the higher the leptin levels

Leptin

- **Leptin** is a protein produced by fat cells. Leptin travels to the brain to **induce satiety**.
- **Leptin receptors** are also present on other cell types including T-lymphocytes and macrophages.
- Leptin **biases the immune response toward the T_H1 (i.e., IFNγ-producing) phenotype.**
- A **mouse with mutation of the *leptin* gene (*ob/ob*)** results in leptin-deficiency □ insatiable appetite and marked obesity.
- Leptin-deficient mice are more susceptible to *MTB* (Wieland C et al. Int Immunol 2005) and *M. abscessus* (Ordway DJ et al. J Leuk Biol 2008).

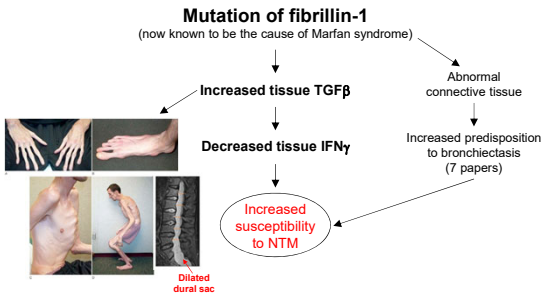
Patients with NTM-LD have lost the normal direct relationship between body fat and leptin levels



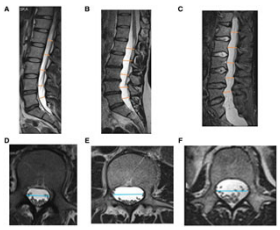
3. Is there a genetic basis for pNTM patients with the Lady W phenotype?

original and may still be valid

Our hypothesis



Is there a link between dural ectasia and bronchiectasis?



Normal | Idiopathic bronchiectasis | Marfan

- **L1-L5 dural sac diameter (DSD)** was analyzed in subjects with:
  - No lung disease (n=72)
  - Idiopathic bronchiectasis (n=71)
  - CF (n=29)
  - MFS (n=24)
- The **L1-L5 DSD was significantly larger in idiopathic bronchiectasis** compared to controls ($p<0.001$) and to CF ($p=0.002$).
- **Strong direct correlation between L1-L5 DSD and presence of NTM-LD** ($p=0.007$) **and long fingers** ($p=0.003$).
- A trend toward increased DSD with scoliosis and family history of idiopathic bronchiectasis.

Daniels ML et al. Ann Am Thorac Soc 2016

NTM-LD: A multigenic disease

- Whole exome sequencing (WES) of 15 NTM-LD patients (from 9 families), 18 unaffected family members, and 54 sporadic NTM-LD patients.
- Compared their WES data to control sequencing data from the 1000 Genomes Project of 300+ Caucasian subjects.
- No dominant gene variant ("mutation") found.
- Candidate gene analysis using the following gene categories:
  - **Connective tissue gene mutations**: NTM-LD = family members $\overset{*}{>}$ controls
  - **Ciliary gene mutations**: NTM-LD $\overset{*}{>}$ family members ≥ controls
  - **Immune gene mutations**: NTM-LD $\overset{*}{>}$ family members = controls
  - ***CFTR* gene mutations**: Family members > NTM-LD $\overset{*}{>}$ controls

*p<0.05

Szymanski EP et al. AJRCCM 2015

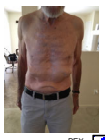
Whole Exome Gene Sequencing of 11 NTM-LD$^{PEX/scoliosis}$ patients

Patient number	Study No.	%body fat or BMI	PEX	Scoliosis	Key gene variant found
1	63682	21%	Yes	Yes	*Δfibrillin-1, ΔIFNγR1*
2	63690	21%	Yes	Yes	***ΔMST1R***
3 (sister of 2)	63685	17.5 kg/m^2	Yes	Straight back	***ΔMST1R***
4	63688	25%	Yes	Yes	
5	63683	21.5 kg/m^2	Yes	Yes	*ΔTGFβ-induced*
6	63687	28%	Yes	Yes	
7	63684	25%	Yes	Yes	
8	63686	27%	Yes	Yes	
9	63692	25%	Yes	Yes	***ΔMST1R***
10	63691	21 kg/m^2	Yes	Yes	***ΔMST1R***
11	63689	23 kg/m^2	Yes	Yes	

MST1R = Macrophage Stimulating-1 Receptor, aka RON (recepteur d'origine nantais)

Targeted Sanger sequencing of 29 pNTM patients without PEX or scoliosis do NOT have ΔMST1R

Familial analysis of two sisters (Patients 2 and 3) with *ΔMST1R*



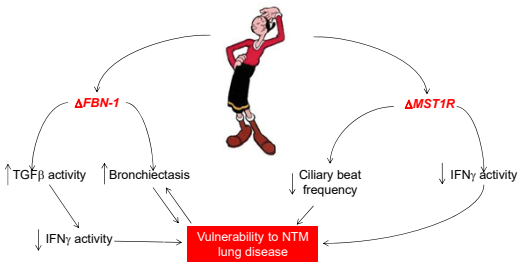
Summary: 5 of 6 sibs have ΔMST1R; 4 of 5 with ΔMST1R have chronic respiratory symptoms

MST1R is known to enhance airway ciliary function!

- MST1R is a **cell surface receptor with tyrosine kinase activity**, expressed on the **apical surface of human ciliated airway and oviduct epithelia**.
- Macrophage-stimulating protein (MSP) is the ligand to MST1R. Addition of MSP to human nasal ciliated epithelium significantly increases ciliary beat frequency.
- MSP is significantly increased in sputa of patients with bronchiectasis compared to normal controls, perhaps a "compensatory measure."

Sakamoto O et al. Role of macrophage-stimulating protein and its receptor, RON tyrosine kinase, in ciliary motility. J Clin Invest 1997.
Takano Y et al. Elevated levels of macrophage-stimulating protein in induced sputum of patients with bronchiectasis. Respir Med 2000.

Graphic summary of the hypothesized mechanisms of how *FBN-1* and *MST1R* mutations may predispose to NTM-LD



Summary

- **Host risk factors** for NTM infections varies depending on the **site of the NTM infection**.
- Those with **skin and soft tissue** NTM infections are due to inoculation from an environmental source or contaminated medical equipment or medication + trauma-associated immunosuppression (*locus minoris resistentiae*).
- Underlying structural lung disease (emphysema, bronchiectasis) is the greatest risk factor for **NTM-LD**. In those without obvious risk factors, it may be due to multigenic causes.
- Those with **extrapulmonary visceral / disseminated disease** are either being treated with an immunosuppressive, have an underlying acquired or genetic cause of immunodeficiency, or both.