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REMINGTON WINTER COURSE IN ID

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NONTUBERCULOSIS MYCOBACTERIA AND BRONCHIECTASIS:

THE CHICKEN AND THE EGG

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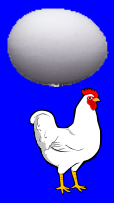
NTM AND BRONCHIECTASIS (BXSIS): THE CHICKEN AND THE EGG

OR



NTM AND BRONCHIECTASIS (BXSIS): THE CHICKEN AND THE EGG

- In some cases NTMs invade pre-existing BXSIS
- In other cases NTMs initiate and propagate BXSIS

NTM AND BRONCHIECTASIS (BXSIS): THE CHICKEN AND THE EGG

Pre-existing Bronchiectasis and Vulnerability to NTM Infection:

*Classic CF

*Prior histoplasmosis (or TB)

*Sarcoidosis

*IPF

*Congenital tracheobronchomegaly (Mounier-Kuhn)

NTM AND BRONCHIECTASIS (BXSIS): THE CHICKEN AND THE EGG

NTM, a Brief History:

1882: Koch's stain and culture of *M. tuberculosis*

Early 20th Century: infrequent recovery and identification of NTM

1950 -1980: sporadic case series in US, Europe and Japan

- mainly men with COPD or silicosis
- mostly in SE of United States

1980 onward: rising cases/awareness

- MAC 2nd most common OI in AIDS
- increasing pulmonary disease in women

NTM AND BRONCHIECTASIS (BXSIS): THE CHICKEN AND THE EGG

NTM Lung Disease: Diagnostic Criteria

-Unlike TB, not all (+) cultures = disease

- American Thoracic Society and IDSA Statement, 2007:

1. Clinical: pulmonary +/- constitutional symptoms

2. Radiographic: cavity on CXR or bronchiectasis on CT scan

3. Microbiologic: 2 or > sputum cultures or 1 (+) BAL

(AJRRCM, 2007:175:367)

NTM AND BRONCHIECTASIS (BXSIS): THE CHICKEN AND THE EGG

What percentage of lab NTM isolates = "disease"?

- Varies by species: Likely: *M. kansasii, MAC, M. abscessus*

  Possible: *M. xenopi, M. malmoense, M. simiae*

  Unlikely: *M. gordonae*

- Recent series: Ontario ≅ 33% *(Marras, Thorax, 2007)*

  Nijmegen≅ 25% *(van Ingen, Thorax, 2009)*

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NTM Lung Disease: Epidemiology

- Not reportable; thus, data fragmentary
- Recent data from Ontario are instructive:

A single lab identifies > 90% of NTM isolates in Province

Reported "isolation prevalence" from 1997-2003.

Rates of NTM recovery rose from 9.1/100T in 1997 to 14.1/100T in 2003

(Marras, Thorax 2007; 62:661-6)

NTM AND BRONCHIECTASIS (BXSIS): THE CHICKEN AND THE EGG

Comparison of the Prevalence of NTM-LD in Ontario Province:

2003: 657 cases of TB *vs.* 430 cases of NTM-LD

Incidence TB = 5.4/100T/yr; NTM = 3.5/100T/yr

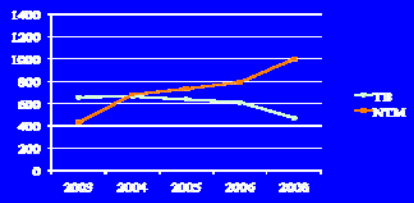
Outcomes over time:

Assumptions -	**TB**	**NTM**
Cure	85%	50%
Duration	~8 mos.	18-24 mos.
Re-Rx	5-10%	30-50%
Usual Sx	<1 mo.	Nearly continual
Expense:	$	$$$$$

Iseman and Marras: AJRCCM; 178:999-1001 (2008)

NTM AND BRONCHIECTASIS (BXSIS): THE CHICKEN AND THE EGG

Hypothetical Model of Prevalences of NTM *vs* TB, Ontario



NTM AND BRONCHIECTASIS (BXSIS): THE CHICKEN AND THE EGG

If the prevalence of NTM-LD exceeds that of TB,
and
If the number of NTM symptomatic days far exceeds TB,

and
If the costs of NTM treatment are orders > than TB,

and
If NTM are mainly acquired from potable water?

WHY ISN'T THIS A MAJOR PUBLIC HEALTH ISSUE?

NTM AND BRONCHIECTASIS (BXSIS): THE CHICKEN AND THE EGG

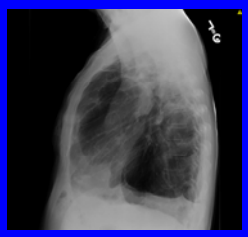
Radiographic features of NTM Lung Disease:

- Prototypic male with COPD: gross cavitation, upper lobe(s)

- Slender woman: bronchiectasis of RML +/or lingula

NTM AND BRONCHIECTASIS (BXSIS): THE CHICKEN AND THE EGG

PA



Lateral

NTM AND BRONCHIECTASIS (BXSIS): THE CHICKEN AND THE EGG

PA

Lateral

NTM AND BRONCHIECTASIS (BXSIS): THE CHICKEN AND THE EGG

CTS RML/Ling BXSIS

CTS Tree-In-Bud

NTM AND BRONCHIECTASIS (BXSIS): THE CHICKEN AND THE EGG

If the NTM are widely distributed in environment (soil and water), why do only some develop disease?

- Less competent pathogens than TB
- Require host complicity:
  - COPD or silicosis
  - Cystic fibrosis, classical or variant
  - Alpha-1 anti-trypsin anomalies
  - GERD/aspiration
  - Primary Ciliary Dyskinesia
  - Rarely, immune deficiency (CVID, CGD)
  - Previous X-ray therapy (breast Ca, lymphoma)
  - The slender female

NTM AND BRONCHIECTASIS (BXSIS): THE CHICKEN AND THE EGG

The Mysterious Female Phenotype:

- Tall
- Slender
- Caucasian (Asian)
- Scoliosis
- Pectus Excavatum
- Mitral valve prolapse

} "Lady Windermere"…not!

(Am Rev Resp Dis, 1991; 144:914-916)
(Am J Resp Crit Care Med, 2008; 178:1066-1074)

NTM AND BRONCHIECTASIS (BXSIS): THE CHICKEN AND THE EGG

NIH Report of Distinctive Morphotype in Cohort of 63 NTM Cases:

*Primarily middle-aged white women; comparison NHANES
*Taller than average (164.7 *vs.* 161 cm)
*More slender than average (21.1 *vs.* 26.8 BMI)
*Higher prevalence of scoliosis (51%)
*Higher prevalence of pectus excavatum (11%)
*Higher prevalence of mitral valve prolapse (9%)

Kim et al; AJRCCM; 2008; 178:1066-1074

NTM AND BRONCHIECTASIS (BXSIS): THE CHICKEN AND THE EGG

NIH Report of Distinctive Morphotype in Cohort of 63 NTM Case:

Other interesting findings:

*36% had CFTR mutations
*Extensive surveys of CMI did not identify defects
*Lady Windermere NOT! Majority coughed chronically
*AAT levels WNL, but phenotypes not determined

Kim et al; AJRCCM; 2008; 178:1066-1074

NTM AND BRONCHIECTASIS (BXSIS): THE CHICKEN AND THE EGG

HYPOTHESIS #1:

- These slender women have subtle anomalies of their connective tissue that make them more vulnerable to NTMs and bronchiectasis
- Possible mechanisms:
  - Airway collapse renders coughs ineffectual
  - Airways subject to distension with cough
  - TGF-Beta effects on CMI

NTM AND BRONCHIECTASIS (BXSIS): THE CHICKEN AND THE EGG

Where do the NTMs come from?

- The NTMS are variably found in the environment (water and soil)
- Falkinham (VA Tech) has found that MAC is found with increasing density in distal water distribution systems

HYPOTHESIS #2:

- NTMs enjoy competitive advantage over coliforms due to resistance to chlorination; symbiotic with non-pathogenic amoeba in biofilms
- Lowered temps in water heating (mandated cap at 125°) has favored survival of the NTMs

NTM AND BRONCHIECTASIS (BXSIS): THE CHICKEN AND THE EGG

What else has promoted NTM lung disease?

HYPOTHESIS #3

- Over the past 3-4 decades we have switched from tub-bathing to showering.
- Shower stalls are increasingly enclosed
- We all regularly inhale MAC (± other NTMs) as we shower

NTM AND BRONCHIECTASIS (BXSIS): THE CHICKEN AND THE EGG

OK, we are all exposed; why more MAC in women?

SPECULATION:

- Hormonal: a. testosterone > estrogen for CMI *vs* NTMs

  b. normal estrogen > low estrogen for CMI

- Leptin: Satiety regulator (↓appetite with fat accumulation); promotes CMI but↓↓ in thin persons

NTM AND BRONCHIECTASIS (BXSIS): THE CHICKEN AND THE EGG

BRONCHIECTASIS: THE GIFT THAT KEEPS ON GIVING:

Whether NTM invades pre-established bronchiectasis, or

Whether NTM is the primary cause of bronchiectasis,

Once bronchiectasis is established in dependent lung zones, the patient is predisposed to recurrent infections (NTM & GNR) for life

NTM AND BRONCHIECTASIS (BXSIS): THE CHICKEN AND THE EGG

Diagnosis and Treatment of NTM Infections:

1. ATS Guidelines: AJRCCM, v 175:367-416 (2007)
2. Key Diagnostic Criteria (Cliff Notes)
   a. Symptoms
   b. Abnormal CXR (cavity) or CTS (bronchiectasis)
   c. Two or more (+) sputum cultures for common pathogens
   d. One (+) bronchoscopy culture
3. Plus a healthy dose of clinical judgment!

NTM AND BRONCHIECTASIS (BXSIS): THE CHICKEN AND THE EGG

Diagnosis and Treatment of NTM Infections (cont'd.)

4. Treatment of NTM Disease*
   a. MAC: macrolide, rifamycin, and EMB, ± SM
   b. *M. kansasii*: INH, RIF, and EMB (?macrolide)
   c. RGM: imipenem or cefoxitin and AK (?macrolide)
   d. Surgery? (unproven but potentially useful)

*Not all with NTM disease need to be treated; but, all should be followed.

THE IMPORTANCE OF NONTUBERCULOUS MYCOBACTERIAL LUNG DISEASE

NATIONAL JEWISH CONSULTATION AND REFERRAL SERVICES

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