Not What They're Not, but What They Are: Nontuberculous Mycobacteria and NTM Infections

Clinical Perspective

Toronto Invasive Bacterial Diseases Network Education Day
November 21, 2019

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Toronto Western Hospital / University Health Network

Financial disclosures

- Site investigator
  - Insmed
- Consultant
  - Insmed, RedHill, Horizon, Spero
- CME
  - Astra Zeneca
  - Novartis

Clinical aspects of NTM Infections

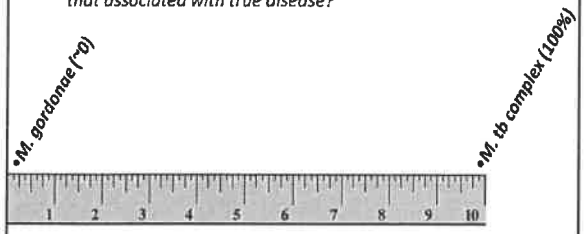
- Objectives

- Pulmonary vs non-pulmonary
- Species relative pathogenicity
- Disease definition
- Risk Factors
- Transmission
- Clinical phenotypes
- Treatment decisions and recommendations
- Outcomes

NTM species

- pathogenic potential (pulmonary)

If someone has NTM isolated from their sputum, how often is that associated with true disease?



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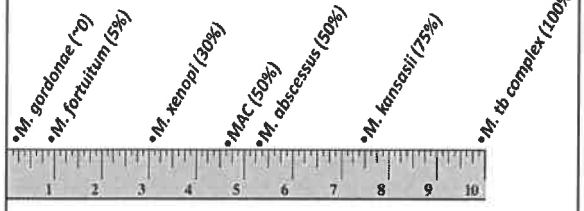

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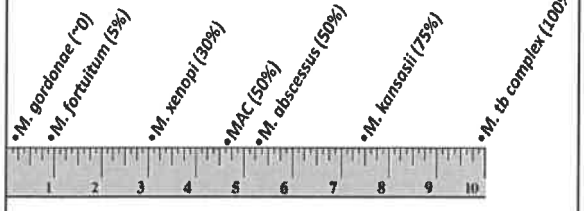

Values neither temporally nor geographically portable!

Box 1 Clinical and microbiological criteria for diagnosing non-tuberculous mycobacterial lung disease (modified with permission from Griffith et al[1])

Clinical (both required)
1. Pulmonary symptoms, nodular or cavitary opacities on chest radiograph, or a high-resolution CT scan that shows multifocal bronchiectasis with multiple small nodules.
and
2. Appropriate exclusion of other diagnoses.

Microbiological
1. Positive culture results from at least two separate expectorated sputum samples. If the results are non-diagnostic, consider repeat sputum AFB smears and cultures.
or
2. Positive culture results from at least one bronchial wash or lavage. *(when sputum cannot be obtained)*
or
3. Transbronchial or other lung biopsy with mycobacterial histopathological features (granulomatous inflammation or AFB) and positive culture for NTM, or biopsy showing mycobacterial histopathological features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture-positive for NTM.

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- Diagnosis

"In the absence of robust evidence to support an alternative definition and due to the clinical and research benefits of having a uniform definition, use of the ATS/IDSA 2007 definition of NTM-PD is recommended."

Howorth et al., Thorax 2017

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Symptoms + Imaging findings + Microbiology = Disease

but

Making the diagnosis of NTM lung disease does not, per se, necessitate starting therapy, which is a decision based on potential risks and benefits for individual patient

Griffith et al., AJRCCM 2007

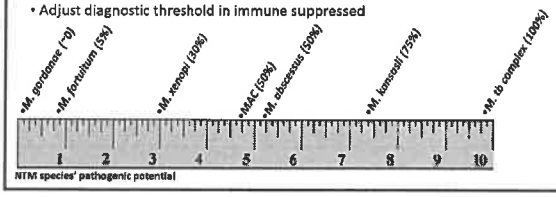
Diagnosis

- Additional considerations

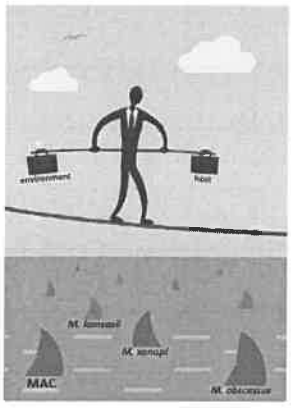
Number of positive specimens
- Disease more likely with increasing number of positive cultures

Species
- Disease likelihood proportional to species pathogenicity

Consider
- High diagnostic threshold for *M. gordonae* (for e.g.)
- Collect more specimens when in doubt
- Adjust diagnostic threshold in immune suppressed

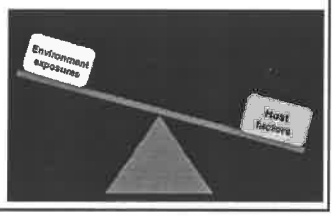


Risk Factors



"Susceptible host" paradigm

– NTM very widespread → exposure extensive
– Disease uncommon (~40/100,000)



NTM PD risk factors

- Age

Region (N studies)	Mean age	
	Overall (weighted)	Range
North America (N=6)	68.2	59-70
Europe (N=12)	62.5	54-66

Prevots,
Clin Chest Med, 2015

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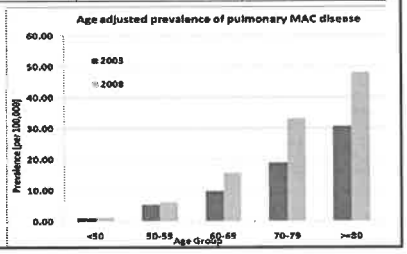
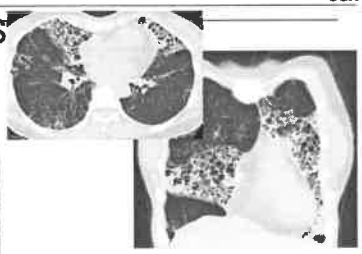


Al-Houqani, Chest 2012

NTM PD risk factors

- sex



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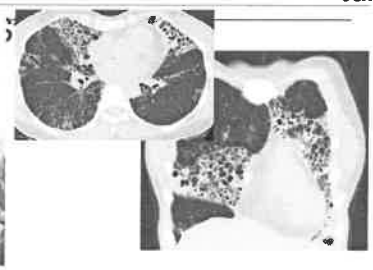


Varies by underlying lung predisposition

- "Idiopathic" bronchiectasis → ~ 85% women
- COPD, fibrosis, etc. → varies by population

Sex distribution NTM PD

- Ontario, Canada

	Species (N)	Female
Ontario population - 2001-2013 (incident NTM-PD)	All (9,681)	51%
	MAC (6,431)	53%
	M. xenopi (2,310)	45%
	M. abscessus (255)	61%
	M. kansasii (162)	33%
TWH NTM clinic – 2003-2018	All (932)	65%

Host factors in Pulmonary NTM

- "Structure vs Function"

Pre-existing structural lung disease

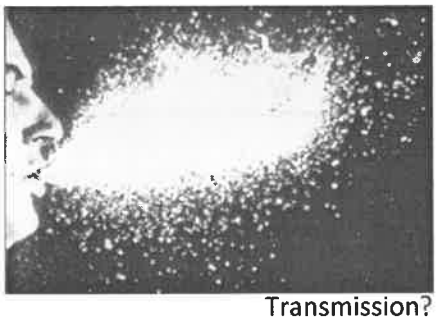
- Emphysema *(Andrejak Thorax 2013, Marras ERJ 2016)*
- Bronchiectasis* (~50% registries, <15% admin database studies)
- Fibrosis (2% IPF patients in Seoul; *Park J Korean Med Sci 2012*)

Covert impairment of muco-ciliary / pulmonary defense

- CFTR mutations (NTM clinic: 20% CF, 50% mutation(s), *Ziedalski Chest 2006*)
- Ciliary impairment
- Immune dysregulation (autoimmunity, medications, etc.)

(Szymanski, AJRCCM 2015)

* Pre-existing typically focal bronchiectasis (post-TB, etc)



Transmission?

Transmissibility?

- Essentially NO public health concerns
- Theoretic risk: high burden patient, close contact with highly susceptible person
- Recent reports:
  - *M. abscessus (ssp. massiliense)*
  - Cystic fibrosis clinics
  - Genotypically identified "outbreaks"
  - Potentially via fomites
    - Patient → environment → patient

Aitken et al. AJRCCM 2012
Bryant et al. Lancet 2013

Transmissibility?

- Undoubtedly rare:
  - No precautions routinely warranted
- Programmatic concerns (high-risk cohorts – CF)
  - Risk uncertain
  - Infection control measures often employed

Source of Infection?

Waters

- Natural - fresh, brown swamp acid, brackish, sea
  (oligotrophic, biofilm formation)

  Falkinham 2009, Gruft 1979
- Engineered – distribution systems, plumbing / fixtures
  (oligotrophic, biofilm, disinfectant-resistance, thermal tolerance)

  Feazel 2009, Falkinham 2011, Thomson 2013

Soils

- Many types – residential, commercial, etc.
  (Particle attachment, oligotrophic, amoebae-resisting, humic and fulvic acid growth stimulation)

  De Groote 2006, Falkinham

Pulmonary NTM

Source of infection - water

Mycobacterium avium in a shower linked to pulmonary disease

Joseph O. Falkinham III, Michael D. Iseman, Petra de Haas and Dick van Soolingen

... *M. avium* isolated from showerhead water and biofilm in the home of a woman with *M. avium* disease. DNA fingerprinting demonstrated identical *M. avium* isolates from showerhead and patient ...

J Water Health 06(2):209–213

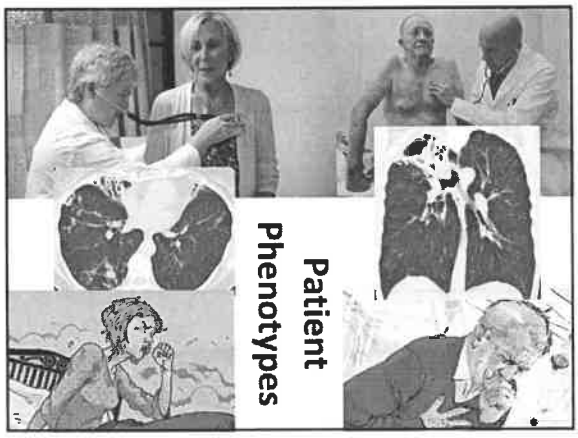
Pulmonary NTM

Source of infection - soil

Case-control
106 pMAC, 53 age-matched controls (bronch^x)
Standardized questionnaires
- **Smoking, EtOH, age at menopause**
- **Exposures – numerous water and soil Qs**

High soil exposure (≥2/wk) more common in cases (24%) vs controls (9%)
- **Univariate - p=0.03**
- **Multivariate OR 5.9 (1.4-24.7, p=0.015)**

Maekawa et al. Chest 2011; 140(3): 723-9



Patient phenotypes

-Structure vs function

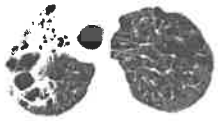
Underlying lung disease
- Emphysema
- Bronchiectasis (prior usually focal)

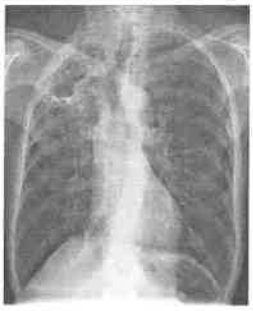
No known underlying lung disease
- Idiopathic → "Lady Windermere"
- Other → recurrent aspiration, etc.

Structure

- emphysema

73 yr old man
- Severe emphysema
- Increasing cough, sputum
- Systemic complaints
- *M. xenopi*

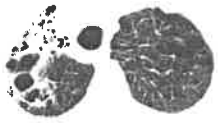




Structure

- emphysema

"Fibrocavitary" disease



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Function

- Idiopathic / Lady Windermere

63 yr old woman, >10 yrs copious sputum

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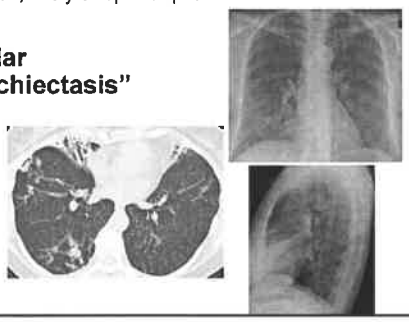
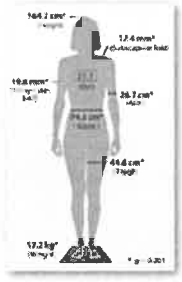
"Nodular bronchiectasis"

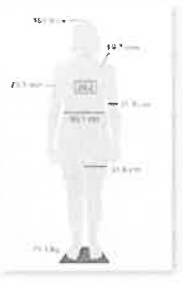


Function

- Idiopathic / Lady Windermere

Patients



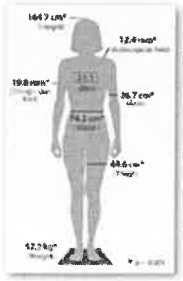


Controls (NHANES age-, sex-, race-matched)

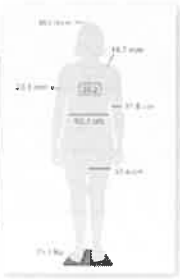
Am J Respir Crit Care Med Vol 178. pp 1066–1074, 2008

Function

- Idiopathic / Lady Windermere



Characteristic		
51%	Scoliosis	2%
11%	Pectus excavatum	1%
9%	Mitral valve prolapse	2%



Am J Respir Crit Care Med Vol 178. pp 1066–1074, 2008

Summary

- Emphysema (structure)

Usually upper lobe, focal, cavitary
Males or females, usually mid-older age

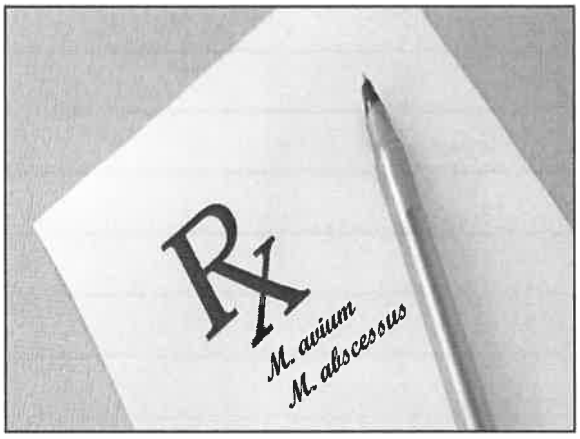
"Fibrocavitary Disease"

Summary

- 'Idiopathic Bronchiectasis' (function)

Usually mid-lung bronchiectasis, centrilobular nodules (may cavitate); Females >> Males, usually mid-older age

"Nodular Bronchiectatic Disease"



ATS / IDSA guidelines

- Diagnosis & Treatment

Symptoms
Imaging
+ Cultures
= Disease

"Making the diagnosis of NTM lung disease does not, per se, necessitate the institution of therapy, which is a decision based on potential risks and benefits of therapy for individual patients"

- ATS / IDSA 2007

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Starting treatment for NTM-PD

- considerations

Diagnostic criteria

Symptoms of NTM
-Local
-Systemic
-Progressive

Imaging
-*Cavitation*
-Extent
-Severity
- Progression

Microbiological burden
- Multiple positives
AFB positive

Other factors

Comorbid illness

Toxicities of prior therapy

Patient wishes
-Aggressive vs conservative
-Aim of Treatment

Other meds
- Interactions
- Pill burden

Clinical relevance
- Species
- Immune suppression

Detailed discussion ± observation, often several visits

Shared decision

Goals of treatment

- guidelines

Regimen choice depends on treatment goals:

- Aggressive therapy appropriate ... when improvement is important and feasible
- Less aggressive therapy appropriate with indolent disease, drug intolerance, potential drug interactions

"...cure may not possible, especially for older, frail individuals with comorbidities and difficulty tolerating multidrug regimens. For these patients, MAC is a chronic, usually indolent, incurable disease, and less aggressive/suppressive treatment may be appropriate."

-Griffith et al. AJRCCM 2007

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Setting goals of therapy – eradication versus suppression
Depends largely on extent of destroyed lung, treatment tolerance

Why is this difficult?

Bugs & Drugs

- **NTM inherently resistant to most available antimicrobials**
- **Requires multiple agents for prolonged periods**
- **Multiple drugs, long duration → many toxicities**

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Short term outcomes
- MAC "success"
  - 60% (Kwak, CID 2017)
  - 71-86% (Jeong, AJRCCM 2015; Wallace, Chest 2014)

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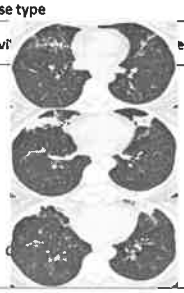
- MAC "success"
  - 60% (Kwak, CID 2017)
  - 71-86% (Jeong, AJRCCM 2015; Wallace, Chest 2014)

Long term outlook
- Persistent predisposition and environmental exposures
- Recurrence:
  - ~30% - 14 mo (Koh 2017)
  - ~50% - 4 years (Wallace 2014)

ATS / IDSA guidelines

- Drug treatment – MAC

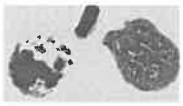
Drug / class	Disease type: Nodular bronchiectasis	Disease type: Cavi… ent
MACROLIDE	Clari 1000 tiw *or* Azi 500 tiw	
Ethambutol	20-25 mg/kg tiw	
Rifamycin	RMP 600 tiw	
Amikacin	Not recommended	



tiw – thrice weekly, qd – once daily
Azi - azithromycin, clari - clarithromycin, RMP – rifampin, RBT - rifabutin

ATS / IDSA guidelines

- Drug treatment – MAC

Drug / class	Disease type	
	Nodular bronchiectasis	Cavitary or Advanced
MACROLIDE		Clari 500-1000 qd *or* Azi 250-300 qd
Ethambutol		15 mg/kg/d
Rifamycin	RMP 600 tiw	RMP 450-600 qd *or* RFB 150-300 qd
Amikacin	Not recommended	Consider / recommended (10-15 mg/kg/d)

tiw – thrice weekly, qd – once daily
Azi - azithromycin, clari - clarithromycin, RMP – rifampin, RBT - rifabutin

ATS / IDSA guidelines

- Other agents – MAC

- Fluoroquinolone
  - Moxifloxacin ~400 qd
  - Levofloxacin ~500 qd
  - Ciprofloxacin ~500 bid
- Clofazimine ~100 mg qd
- Linezolid ~600 mg qd

Pulmonary MAC

- Drug susceptibility testing

Interpretation unclear for most drugs, except...

- Macrolides:
  - Resistance (MIC ≥32 ug/mL) → poor response / outcomes

Pulmonary MAC

- Drug susceptibility testing

Interpretation unclear for most drugs, except...

- Macrolides:
  - Resistance (MIC ≥32 ug/mL) → poor response / outcomes
- Amikacin (IV):
  - Susceptible MIC ≤16 ug/mL
  - Int MIC 32 ug/mL
  - Resistant MIC ≥64 ug/mL
  - Resistance associated with treatment failure despite amikacin administration

    Brown-Elliot, J Clin Micro 2013
  - RCT of inhaled amikacin → no patients with isolate MIC >64 converted their sputum

    Olivier, AJRCCM 2016

Pulmonary MAC

- Drug susceptibility testing

Interpretation unclear for most drugs, except...

- Macrolides
- Amikacin
  - Request susceptibility if:
    - Starting treatment
    - Prior extensive macrolide / aminoglycoside use
    - Poor treatment response
    - Recurrence

Ignore MIC for EMB → DON'T stop EMB because MIC high...

Pulmonary MAC

- Drug susceptibility testing

Interpretation unclear for most drugs, except...

- Macrolides
- Amikacin
  - Request susceptibility if:
    - Starting treatment
    - Prior extensive macrolide / AG use
    - Poor treatment response
    - Recurrence

Ontario, 2010-15, DST request rates:

MAC – 6.3%
- **24% of cases in ON were treated**

***M. abscessus* – 36.2%**

***M. xenopi* – 1.8%**

Resistance rates MAC:
- **Macrolide 8%**
- **Amikacin 23% (MIC ≥64)**

Andrews et al., JAMMI in press

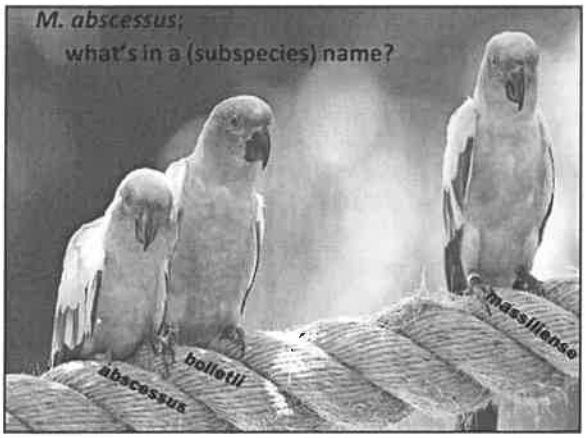
Ignore MIC for EMB → DON'T stop EMB because MIC high...

ATS / IDSA guidelines

- Drug treatment duration

At least 12 months of culture negative sputum

(shorter treatment duration → increased early recurrence)



M. abscessus

- ssp. abscessus, massiliense, bolletii

- Extensively resistant to many antimycobacterial drugs
- Likely most difficult NTM to treat
- Uncertain
  - Natural history
  - Optimal treatment strategy
    - When
    - How many / which drugs
    - How long
  - Reliability of DST
    - Important (macrolide, amikacin > others)

M. abscessus

- ssp. abscessus, massiliense

Clinical Significance of Differentiation of *Mycobacterium massiliense* from *Mycobacterium abscessus*

Won-Jung Koh[1*], Kyeongman Jeon[1*], Nam Yong Lee[2], Bum-Joon Kim[3], Yoon-Hoh Kook[3], Seung-Heon Lee[4], Young Kil Park[4], Chang Ki Kim[4], Sung Jae Shin[5], Gwen A. Huitt[6], Charles L. Daley[6], and O. Jung Kwon[1]

Am J Respir Crit Care Med Vol 183. pp 405–410, 2011

TABLE 3. TREATMENT RESPONSES FOR PATIENTS WITH *MYCOBACTERIUM ABSCESSUS* AND *MYCOBACTERIUM MASSILIENSE* LUNG DISEASE

	M. abscessus (*n* = 24)	*M. massiliense* (*n* = 33)	*P* Value
Symptomatic response			0.040
Improved	18 (75%)	32 (97%)	
Unchanged	4 (17%)	1 (3%)	
Worsened	2 (8%)	—	
Radiographic response on HRCT			0.003
Improved	10 (42%)	27 (82%)	
Unchanged	7 (29%)	5 (15%)	
Worsened	7 (29%)	1 (3%)	
Microbiologic response			<0.001
Initial sputum conversion and maintenance of conversion	6 (25%)	29 (88%)	
Initial sputum conversion, with sputum relapse	4 (17%)	3 (9%)	
Failure to sputum conversion	14 (58%)	1 (3%)	

M. abscessus

- ssp. abscessus, massiliense

Clinical Significance of Differentiation of *Mycobacterium massiliense* from *Mycobacterium abscessus*

Am J Respir Crit Care Med Vol 183. pp 405–410, 2011

TABLE 4. TEST RESULTS FOR THE PRESENCE OF INDUCIBLE RESISTANCE TO CLARITHROMYCIN OF *MYCOBACTERIUM ABSCESSUS* AND *MYCOBACTERIUM MASSILIENSE*

Isolate	Clarithromycin Resistance (MIC, μg/ml)	No. of Clinical Isolates Day 3	Day 7	Day 14
M. abscessus (*n* = 19)	Susceptible			
	≤0.5	9 (47%)	—	—
	1	6 (32%)	—	—
	2	4 (21%)	—	—
	Intermediate			
	4	—	—	—
	Resistant			
	8	—	1 (5%)	—
	16	—	8 (42%)	—
	32	—	4 (21%)	3 (16%)
	≥64	—	6 (32%)	16 (84%)
M. massiliense (*n* = 28)	Susceptible	20 (71%)	20 (71%)	20 (71%)
	≤0.5			
	1		8 (29%)	8 (29%)
	2	—	—	—
	Intermediate			
	4	—	—	—
	Resistant			
	≥8	—	—	—

M. abscessus

- ssp. abscessus, massiliense, bolletii

Intact *erm*41 gene responsible for inducible macrolide resistance

rrl gene mutation may confer mutational / constitutive resistance in any *M. abscessus* ssp.

ON Public Health Lab:

- Subspecies - *abscessus, massiliense, bolletii*
- *erm*41 gene – functional (intact/truncated, C28/T28 sequevar - inducible macrolide resistance)
- rrl gene mutation – mutational macrolide R

Request phenotypic DST

- Macrolide + others (AK, cefox, ? imipenem / linez / moxi / clofazimine* / tigecycline)

M. abscessus

- management

Consider clinical, radiological, microbiological features and other patient factors

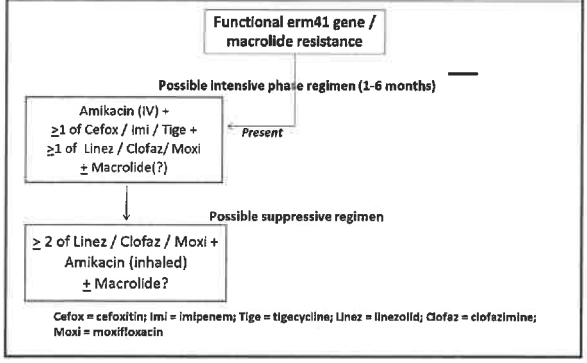
Observation versus treatment

When to initiate antimicrobial therapy

- Progressive or severe infection
- "Eradication" is considered
- Pre-lung transplant
- Unclear if early aggressive therapy in certain patient groups is beneficial

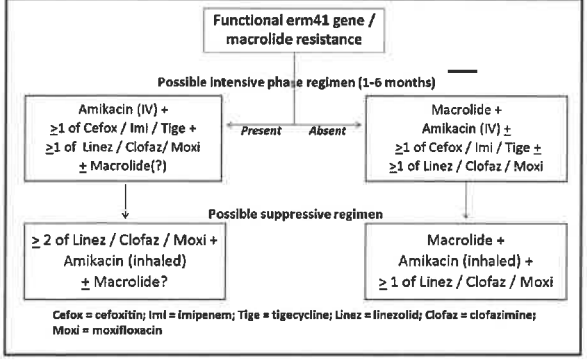
M. abscessus treatment

- Rational antibiotic selection



M. abscessus treatment

- Rational antibiotic selection

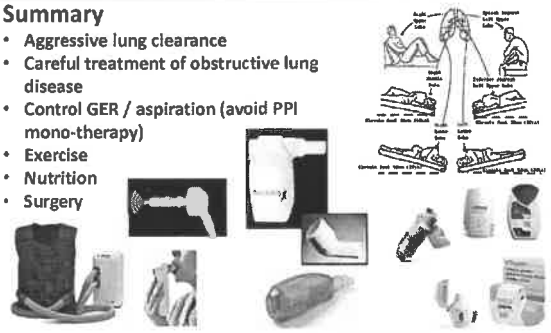


Non-antibiotic treatment

- NTM-PD / bronchiectasis

Summary

- Aggressive lung clearance
- Careful treatment of obstructive lung disease
- Control GER / aspiration (avoid PPI mono-therapy)
- Exercise
- Nutrition
- Surgery



MAC

(Indefinite) Exposure avoidance?

- No hot tub
- Showers?
  - Well ventilated bathroom
  - Shorter showers
  - Clean showerhead
  - Increase home hot water temperature
- Avoid aerosol water exposure
- Gardening / soil precautions?
- Use of use filters

NTM outcomes

- Chronic disease

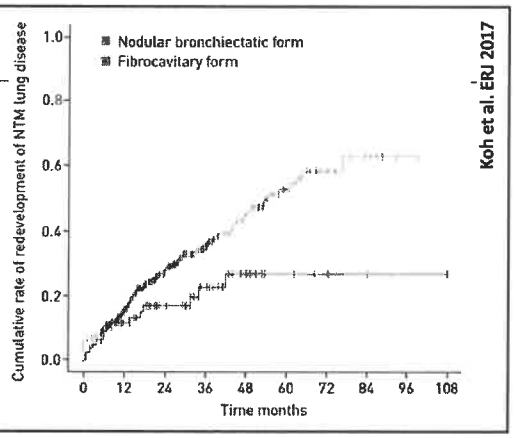
- Minority treated
  - 18% US HMO study *(Prevots, AJRCCM 2010)*
  - 20-24% ON population *(Brode, ATS meeting 2018)*
- Treatment "success"
  - 52-66%* *(Diel, CHEST 2018)*
- Recurrence
  - 14 months – 30% *(Koh ERJ 2017)*
  - 48 mo – 50% *(Wallace, Chest 2014)*
- Of patients refractory / persistent (on therapy)
  - 55% polyclonal from outset
  - 50% acquired new strain / 25% mixed old and new
  - 25% "true refractory" (persistence of initial strain)

(Jhun AJRCCM 2018)

Study Design

NTM outcomes

- Recurrence



Koh et al. ERJ 2017

Pulmonary MAC

- Survival

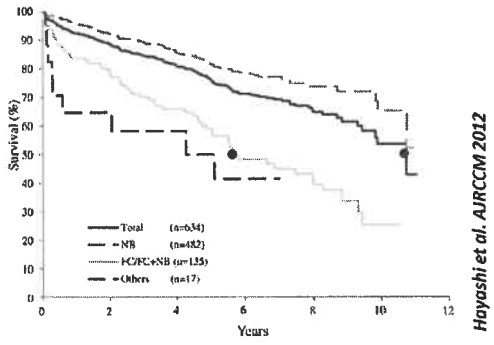
634 patients pMAC

- Mean age 69
- Median follow-up 4.7 years
- 76% nodular bronchiectasis
- 17% fibrocavitary

Hayashi et al. AJRCCM 2012

Pulmonary MAC

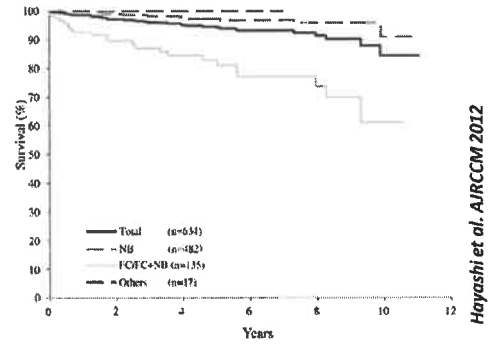
- All cause mortality



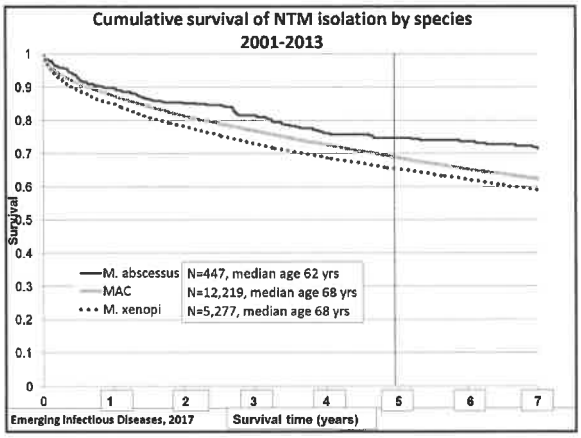
Hayashi et al. AJRCCM 2012

Pulmonary MAC

- pMAC mortality



Hayashi et al. AJRCCM 2012



NTM-PD (ON), Survival by Species, 2001-2013

NTM Species	Value (N=9,681)	Adjusted HR	95% CI	P-value
MAC (reference)	6,323 (65.3%)	-	-	-
M. xenopi	2,263 (23.4%)	1.22	(1.13-1.31)	<.0001
M. fortuitum	265 (2.7%)	1.02	(0.84-1.23)	0.8538
M. abscessus	245 (2.5%)	0.98	(0.78-1.24)	0.8841
M. kansasii	158 (1.6%)	1.25	(0.99-1.57)	0.0636
All other species	427 (4.4%)	0.94	(0.80-1.10)	0.4306

Pop-based, incident NTM

Marras et al, EID 2017

NTM-PD Survival, ON, 2001-2013

Group	Total	1-year Survival	5-year Survival	Hazard ratio (95% CI)
NTM	**8469**	**85.8%**	**65.6%**	**1.63 (1.56-1.70)**
Control	8469	95.0%	78.7%	(ref)
MAC	**5543**	**86.6%**	**66.7%**	**1.57 (1.48-1.66)**
Control	5543	94.8%	78.5%	(ref)
M. xenopi	**1975**	**82.3%**	**59.9%**	**1.84 (1.69-2.01)**
Control	1975	95.0%	77.7%	(ref)
M. abscessus	**201**	**92.0%**	**79.2%**	**1.49 (1.00-2.21)**
Control	201	95.5%	87.3%	(ref)

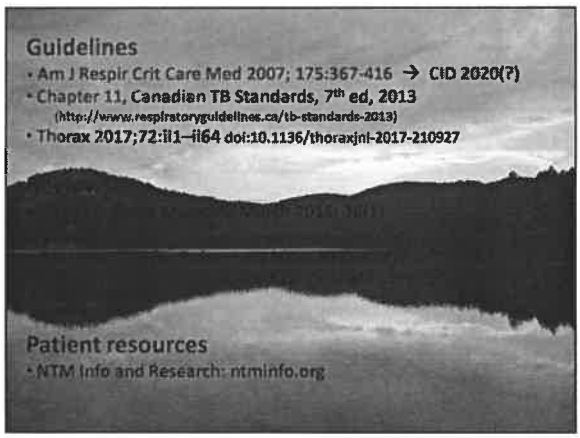
Pop-based, incident NTM, matched by age, sex, index date, propensity score

Marras et al, EID 2017

Clinical aspects of NTM Infections

- Summary

- Pulmonary vs non-pulmonary
- Species relative pathogenicity
- Disease definition
- Risk Factors
- Transmission
- Clinical phenotypes
- Treatment decisions and recommendations
- Outcomes


Guidelines
• Am J Respir Crit Care Med 2007; 175:367-416 → CID 2020(7)
• Chapter 11, Canadian TB Standards, 7th ed, 2013
(http://www.respiratoryguidelines.ca/tb-standards-2013)
• Thorax 2017;72:ii1–ii64 doi:10.1136/thoraxjnl-2017-210927
Patient resources
• NTM Info and Research: ntminfo.org

Thank You!