DM seminar

Pulmonary diseases due to NTM & their management

Content

1. Introduction
2. Microbiology
3. Epidemiology
4. Diseases
5. Diagnosis
6. Treatment
7. Individual species

Introduction

- Genus – Mycobacterium
- Mycolic acid containing genera
- Aerobic, non-spore forming, non motile
- Gram positive Rods
- Discovered for the first time in 1882 by Robert Koch
- More than 200 species
- NTM classification given by Runyon in 1959

Mycobacterium: General Characteristics, Laboratory Detection, and Staining Procedures. In: *Manual of Clinical Microbiology.* Canada: ASM, pp. 536-539.

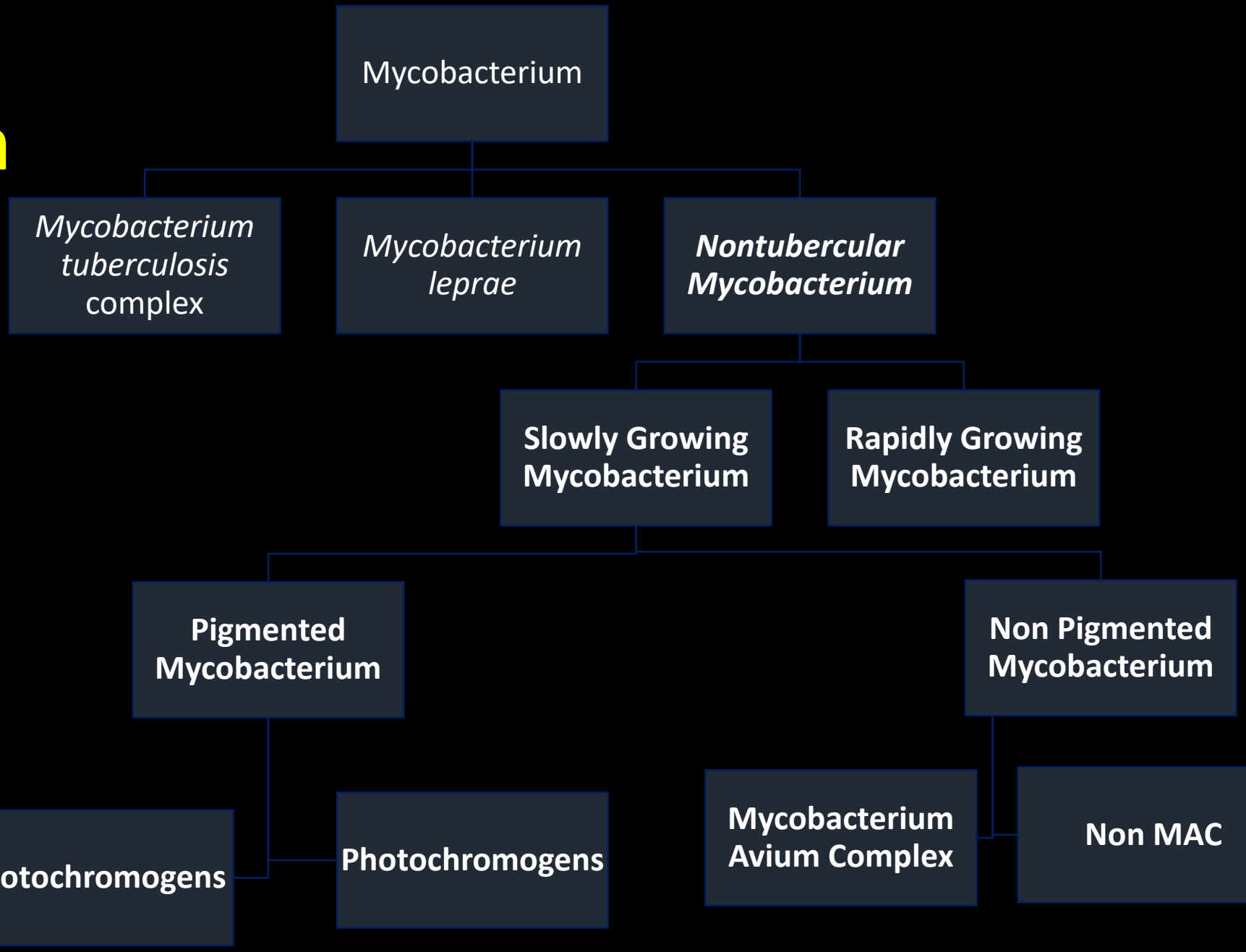
Also known as

- Atypical Mycobacteria
- Mycobacteria other than Tuberculosis (MOTT)
- Potentially pathogenic environmental mycobacteria (PPEM)
- Anonymous Mycobacteria
- Non Tuberculous Mycobacteria

History

1868	Tuberculosis first described in Chicken
1890	Recognized in lab to be distinct from *M. tuberculosis*
	Identified as *M. Avium*
1943	First case of MAC lung disease
1950	Pulmonary disease due to NTM established

Classification



Mycobacterium Tuberculosis. In: *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases.* New york: Elsevier, pp. 2787-2790.

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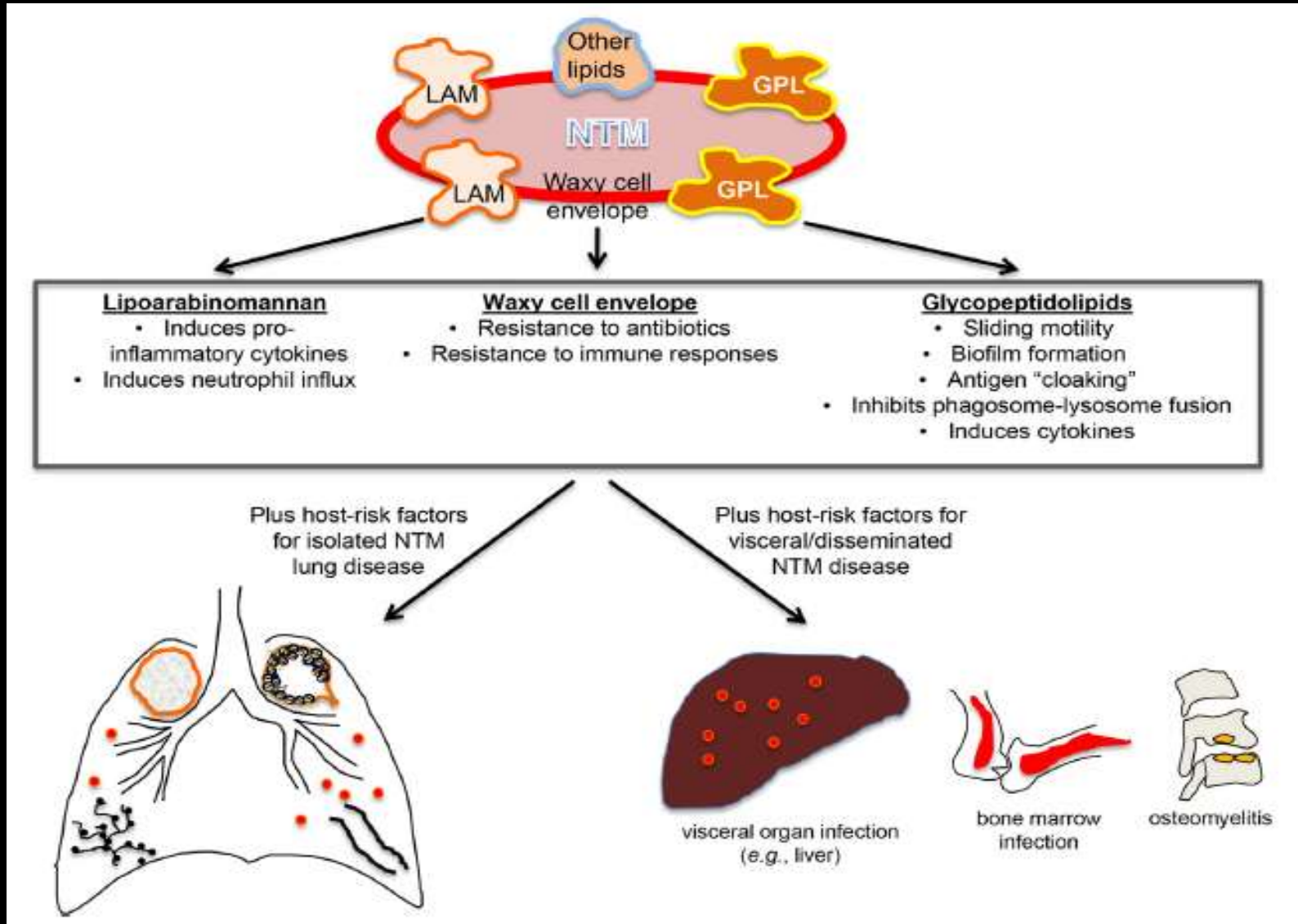
Microbiology

- Staining: Ziehl- Neelsen staining, Auramine Rhodamine
- Culture methods:
    - Sterile specimen can be inoculated directly
    - Non Sterile specimen require chemical decontamination by NaLC-NaOH method
- Solid media: Middlebrook 7H11 and Lowenstein-Jensen
- Liquid media: BACTEC 12 B and MGIT
- Duration: one week for Rapidly growing and 2- 3 weeks for slowly growing
- New techniques for species identification: Nucleic Acid probes, HPLC, PCR- RLPA, 16S Ribosomal DNA sequencing
- Susceptibility testing: Critical concentration method is used

Woods, G. L., 2011. *Susceptibility Testing of Mycobacteria, Nocardiae, and Other Aerobic Actinomycetes,* Wayne : CLSI

Virulence Factors



Mycobacterium: General Characteristics, Laboratory Detection, and Staining Procedures. In: *Manual of Clinical Microbiology.* Canada: ASM, pp. 536-539.

Microbiology: *MAC*

- Rapidly identified on HPLC
- Nucleic acid probes are also commercially available (Accuprobe, GenProbe)
- DST: single concentration DST do not correlate with in vivo responses
- Exception: Macrolides and Amikacin
- Clarithromycin sensitivity should be done in all clinical cases (IIA)
- In Macrolide resistant cases newer Quinolones and Linezolid sensitivity can be done

J Infect Dis. 2002 Jul 15; 186(2):266-73.

Microbiology: *M. Kansasii*

- Slowly growing Mycobacterium- Photochromogenic
- *M. Kansasii* found exclusively in treated water sources
- DST: In vitro Rifampicin sensitivity should be done in all cases (IIA)
- Sensitivity to Rifabutin, Clarithromycin, ethambutol, Fluoroquinolones and aminoglycosides should be done in Rifampicin resistant isolates
- Extremely virulent organism unlike other NTMs

Clin Infect Dis. 1994 May;18(5):736-43

Microbiology: *RGM*

- *M. Abscessus, M. Fortuitum, M. Chelonae*
- Can grow on Blood Agar as well as Chocolate Agar media
- Chemical decontamination should be avoided as they are susceptible
- Inherently resistant to Isoniazid, Ethambutol, Rifampicin
- Inducible macrolide resistance gene (erm) (50S RNA)
- Drug sensitivity test for Imipenem and Aminoglycosides should be done

Abstr Annu Meet Am Soc Microbiol 2005;104.

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Epidemiology

- Soil and water sources (rinsing mouth with tap water)
- Spa, Showers and pools commonly have MAC isolates
- Resistant to conventional decontamination
- Not following manufacturers instructions for cleaning increases risk of growth
- *M. xenopsi, M. mucogenicum, M. simiae and M. Lentiflavum* are usually contaminants
- No evidence of animal to human or human to human transmission

Centers for Disease Control and Prevention. Nontuberculous mycobacteria reported to the public health laboratory information system by state public health laboratories: United States, 1993–1996.

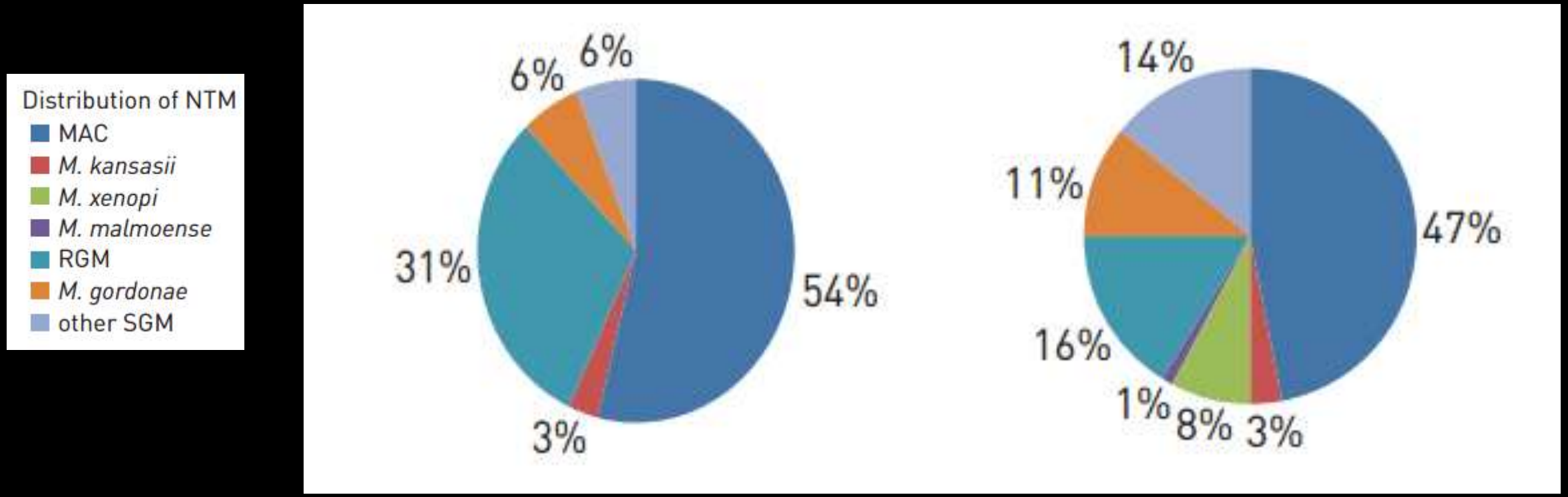
Epidemiology

- Symptomatic disease is due to reinfection instead of reactivation
- MAC is the most common NTM
- Pulmonary disease is the most common manifestation
- Disease burden correlates with bacterial load
- Burden of NTM cases is increasing.

Reasons for increase burden

- Increased susceptibility of individuals
- Improved techniques for primary culture of NTM
- Detection of infection by direct DNA isolation and sequencing

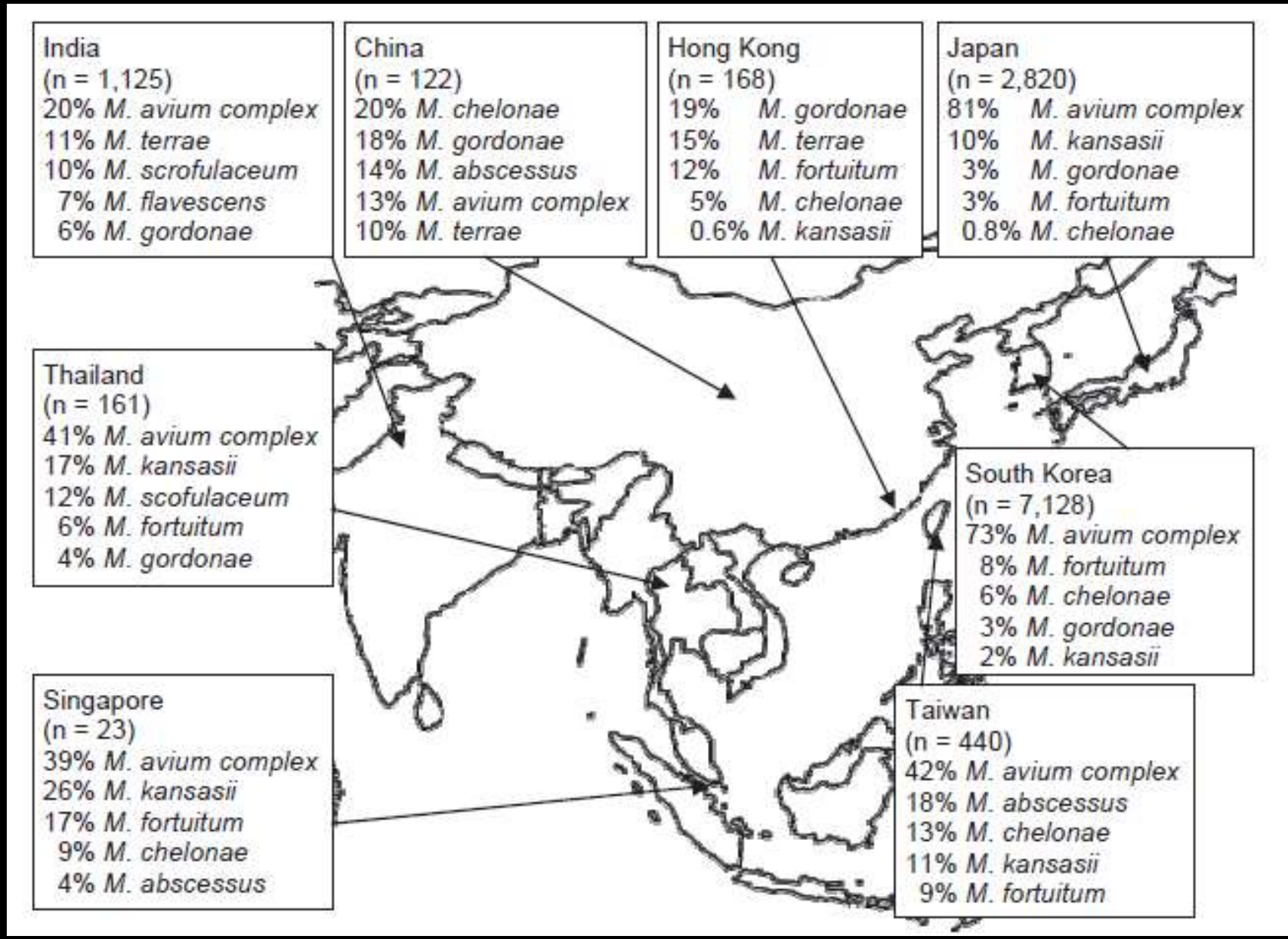
Distribution- Asia Total



Eur Respir J. 2013 Dec;42(6):1604-13

Asian countries

5 most prevalent NTM species found in respiratory specimens (1971-2007)



Emg Inf Diseas J. 2011 Mar;17(3):343-351

Indian epidemiology

- Prevalence- not exactly known
- NTM- not a reportable condition
- Lack of awareness among clinicians
- Lack of laboratory capacity to diagnose these infections

Indian scenario

- 133 isolates of NTM were studied to species levels
- Clinical aspects of the patients were considered
- 81% of the NTM were recovered from pulmonary and 19% from extra-pulmonary specimens.
- SGM: 40% were identified as M. Intracellulare, followed by M. Simiae (35%), M. kansasii (6%)
- RGM: M. fortuitum (41%) and M. abscessus (59%)
- 58 (46%) NTM met clinical, radiological and microbiological criteria.

Int J Tuberc Lung Dis. 2010 Aug;14(8):1001-8.

CMC Vellore

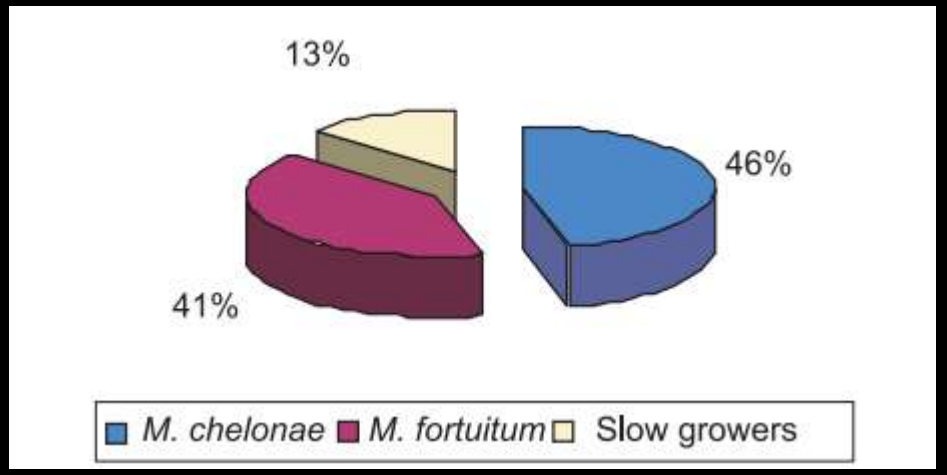


Table: Distribution of NTM from different clinical specimens

Specimens	*M. chelonae*	*M. fortuitum*	*M. szulgai*	*M. terrae*	*M. scrofulaceum*	*M. flavescens*	*M. gordonae*	*M. simiae*	*M. smegmatis*
Biopsy	24	19	-	1	1	1	-	-	-
Sputum	8	6	2	1	-	-	1	1	1
Pus	15	18	-	-	-	-	-	-	-
CSF	3	-	-	-	-	-	-	-	-
Gastric juice	-	3	1	-	-	-	-	-	-
Urine	-	-	-	-	-	-	-	-	1
Blood	3	1	-	-	-	-	-	-	-
Total	**53**	**47**	**3**	**3**	**1**	**1**	**1**	**1**	**2**

Indian J Med Microbiol. 2005 Jul;23(3):172-5.

LRS Institute of TB & Respiratory Diseases

Specimen	Bron-washing	Lymph node	pleural pus	Pl-fluid	CSF	Pus	Ascitic fluid	Sputum	Total
M. pheli	-	1	1	-	1	-	-	2	5
M.simiae	**1**	1	-	2	-	-	-	3	7
M.avium	**1**	1	1	-	-	-	-	3	6
M.fortuitum	-	1	1	1	-	-	-	2	5
M.chelonae	**1**	1	1	-	-	-	-	2	5
M. kansasii	-	1	1	1	-	-	-	2	5
M.gordonae	-	2	1	-	-	-	-	2	5
M.terrae	**1**	1	1	-	-	-	-	1	4
M.vaccae	-	-	1	-	-	-	-	1	2
M.malmoensae	-	-	1	-	-	-	-	1	2
M.trivale	-	1	1	-	-	-	-	-	2
M.flavescens	-	-	1	-	-	-	-	1	2
M.szulgae	**1**	-	1	-	-	-	-	-	2
M.triplex	-	-	-	-	-	-	-	1	1
M.mucogenicum	-	-	1	-	-	-	-	-	1
M.tuscae	-	1	-	-	-	-	-	-	1
M.septicum	-	1	-	-	-	-	-	-	1
M.scrofullacaeum	-	-	-	-	-	-	-	1	1
M.intracellulare	-	-	-	-	-	-	1	-	1
M.xenopi	-	-	-	-	-	1	-	-	1
M.ulcerans	-	-	-	-	-	1	-	-	1
Total	**5**	12	13	4	1	2	1	22	60

(Indian J Tuberc 2013; 60: 71 - 76)

SGPGI

Prevalence of NTM species differentiated by GenoType Mycot acterium CM/AS assay ($n = 62$).

Species of nontubercular mycobacteria	Frequency (%)
M. fortuitum	17 (27.5%)
M. intracellulare	13 (20.9%)
M. abscessus	9 (14.6%)
M. chelonae	8 (12.9%)
M. avium complex	5 (8.1%)
M. kansasii	3 (4.8%)
M. interjectum	2 (3.2%)
M. gordonae	2 (3.2%)
Other NTM	3 (4.8%)

Biomed Res Int. 2015; 2015: 465403.

PGIMER

Indian J Med Res. 1990 Mar;91:111-4.

Isolation rates of different mycobacterial species from Chandigarh (north India).

Chakrabarti A[1], Sharma M, Dubey ML.

Author information

Abstract

A total of 4958 **patients**, clinically suspected to have tuberculosis were screened for mycobacteria by acid fast staining and culture procedures. Mycobacterial species were isolated from 462 (9.3%) **patients** while acid fast bacilli were demonstrated on smear examination in 83 (1.7%) **patients**. Mycobacterium tuberculosis was the most common isolate (92%). Among the nontuberculous mycobacteria, M. fortuitum was isolated in 13 (2.8%), M. avium in 2 (0.4%) and M. szulgai in 1 (0.2%). In 22 individuals clinically suspected of tubercular pleural effusion, pleural biopsy specimen gave higher isolation of mycobacteria (27.3%) as compared to isolations from pleural fluid specimens (9.1%).

Indian J Med Res. 1990 Mar;91:111-4.

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Diseases

- Pulmonary disease
- Hypersensitivity diseases
- Disseminated disease
- Lymphatic disease
- Skin, soft tissue and bone infections

Disease Spectrum

Syndrome	Common Causes	Less-Common Causes
Pulmonary disease (especially in adults)	*Mycobacterium avium-intracellulare*, *M. kansasii*, *M. abscessus*	Uncommon: *M. fortuitum*, *M. malmoense*, *M. szulgai*, *M. scrofulaceum*, *M. smegmatis*, *M. simiae*, *M. xenopi* Rare: *M. celatum*, *M. asiaticum*, *M. shimodei*
Cervical and lymphadenitis (especially children)	*M. avium*, *M. intracellulare*	*M. scrofulaceum*, *M. malmoense*, *M. abscessus*, *M. fortuitum*
Skin and soft tissue disease	*M. fortuitum*, *M. chelonae*, *M. abscessus*, *M. marinum*	*M. haemophilum*, *M. kansasi*, *M. smegmatis*, *M. ulcerans*
Skeletal (bones, joints, tendons) disease	*M. marinum*, *M. avium* complex, *M. kansasii*, *M. fortuitum* group, *M. abscessus*, *M. chelonae*	*M. haemophilum*, *M. scrofulaceum*, *M. smegmatis*, *M. terrae-nonchromogenicum* complex
Catheter-related infections	*M. fortuitum*, *M. abscessus*, *M. chelonae*	*M. mucogenicum*
Disseminated infection	HIV-seropositive host: *M. avium*, *M. kansasii*	*M. haemophilum*, *M. genavense*, *M. xenopi*, *M. marinum*, *M. simiae*, *M. intracellulare*, *M. scrofulaceum*, *M. fortuitum*
	HIV-seronegative host: *M. abscessus*, *M. chelonae*	*M. marinum*, *M. kansasii*, *M. haemophilum*, *M. fortuitum*

Am J Respir Crit Care Med 2007 Feb 15;175(4):367-416.

Pulmonary manifestations

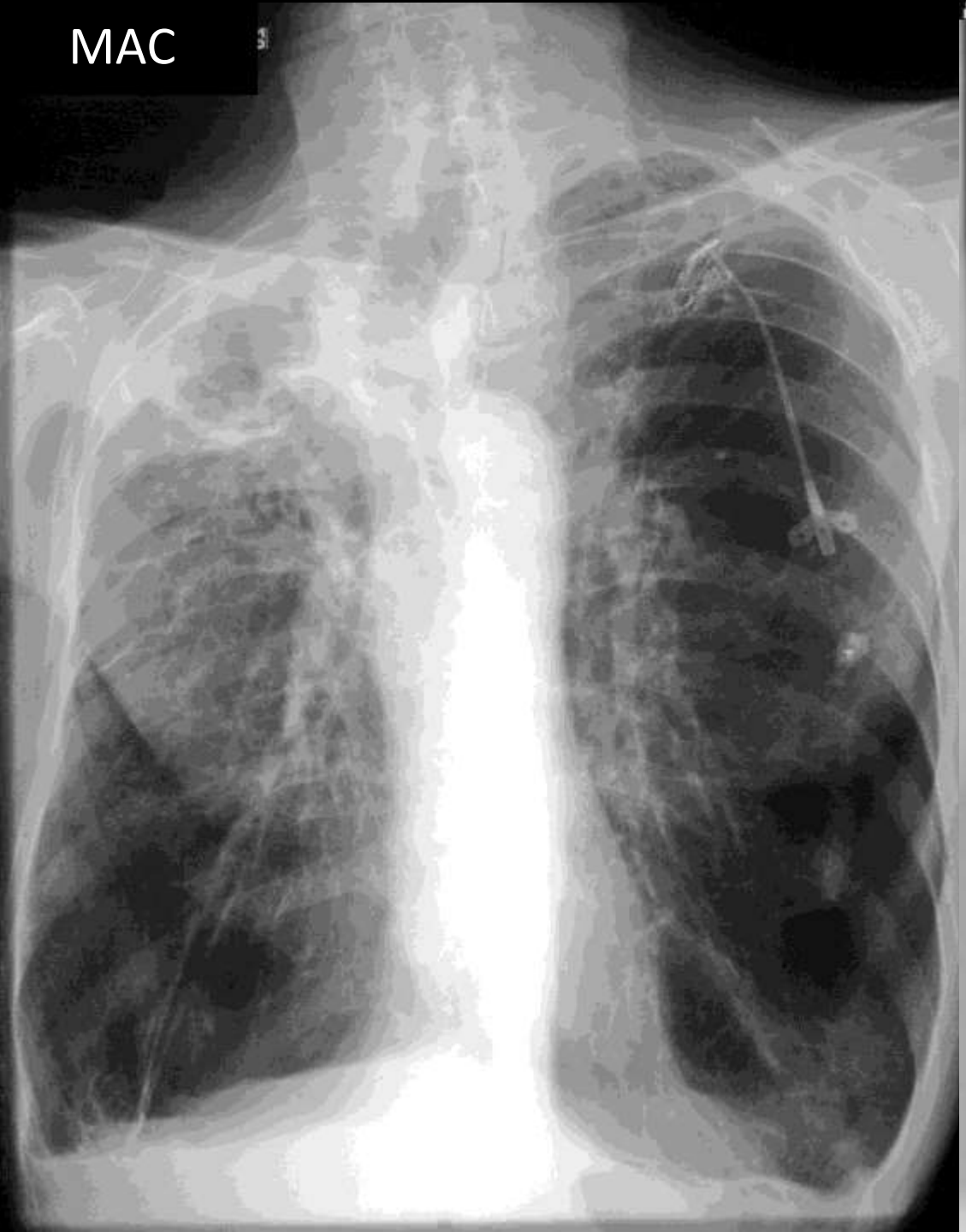
- Most common NTM manifestation
- Risk factors :
    - *Age*
    - *Male*
    - *Low BMI*
    - *Prior lung disease*
    - *Exposure to soil*
    - *Working in water resources*
    - *GERD*

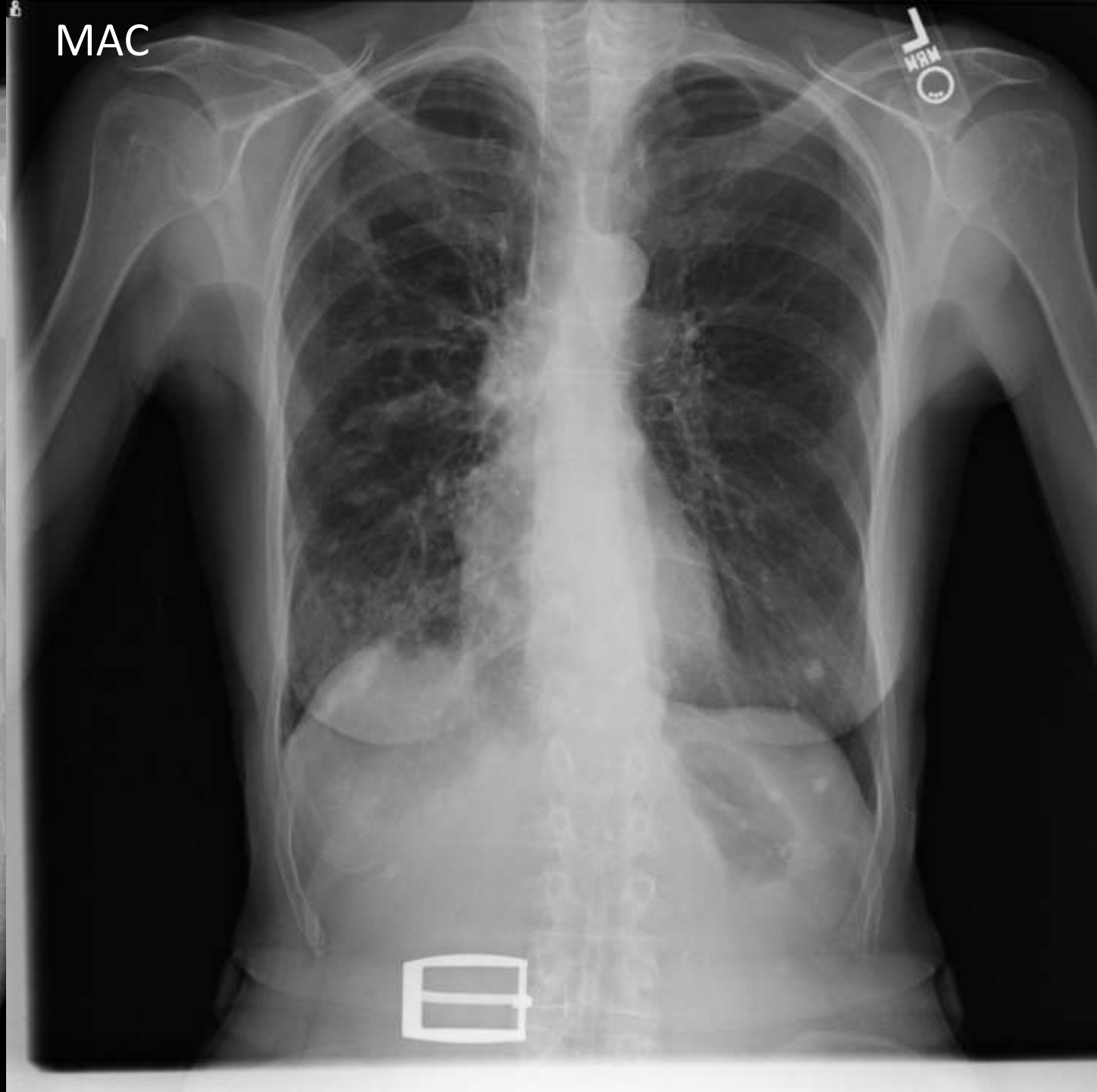
Symptoms

- Chronic cough
- Sputum production
- Fatigue
- Malaise
- Dyspnea
- Fever
- Hemoptysis
- Weight loss

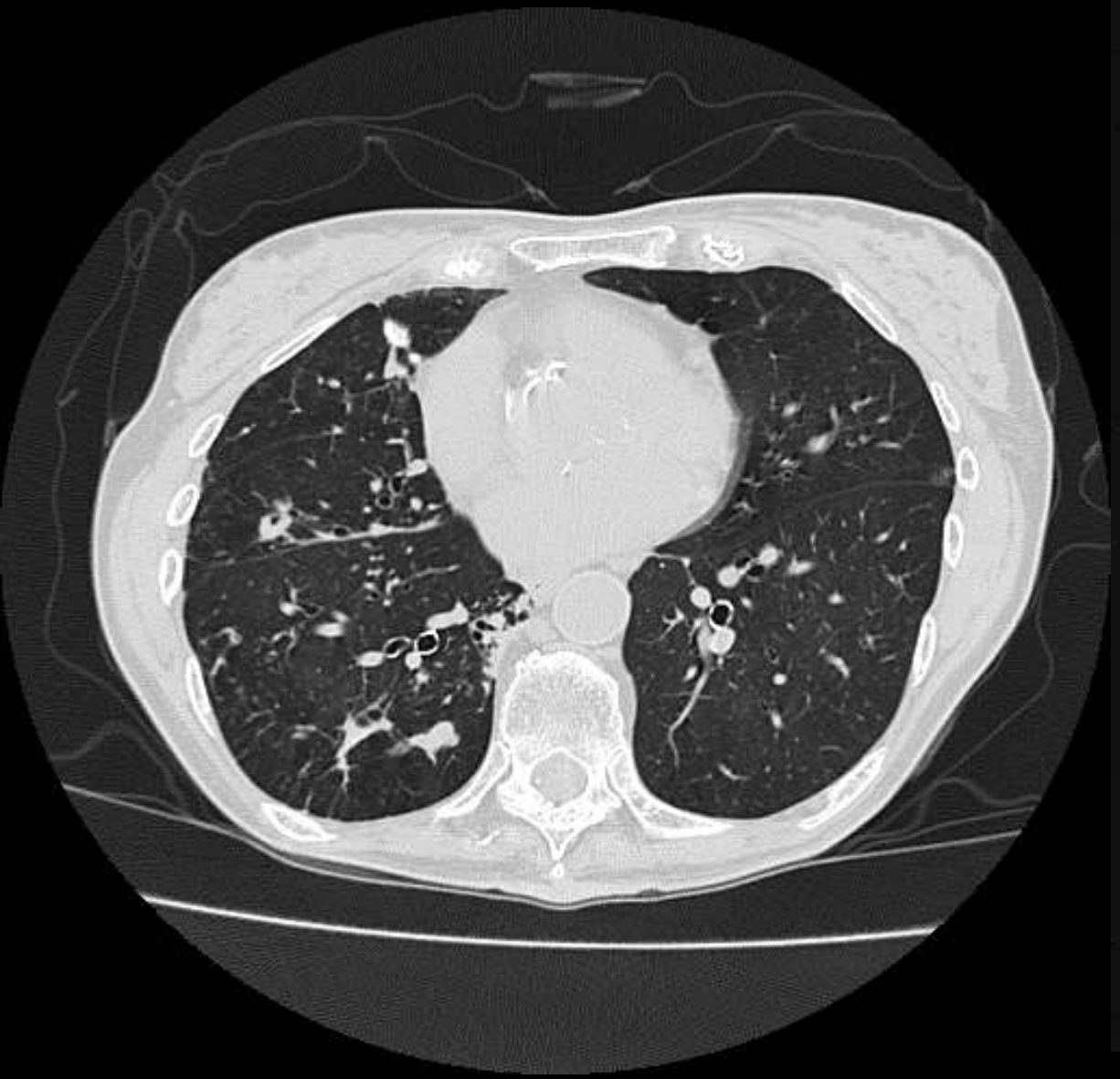
Radiographic changes

- 2 types:
- Fibrocavitatory: Can be evaluated only on Chest X ray basis
    - Thin walled cavities with less parenchymal opacity
    - Less bronchogenic but more contiguous spread
    - Common pleural involvement
- Nodular/bronchiectatic: Need HRCT for evaluation
    - Mid- and lower- lung fields
    - Multifocal bronchiectasis
    - Small (<5 mm) nodules
- Can even cause dense solitary pulmonary nodule

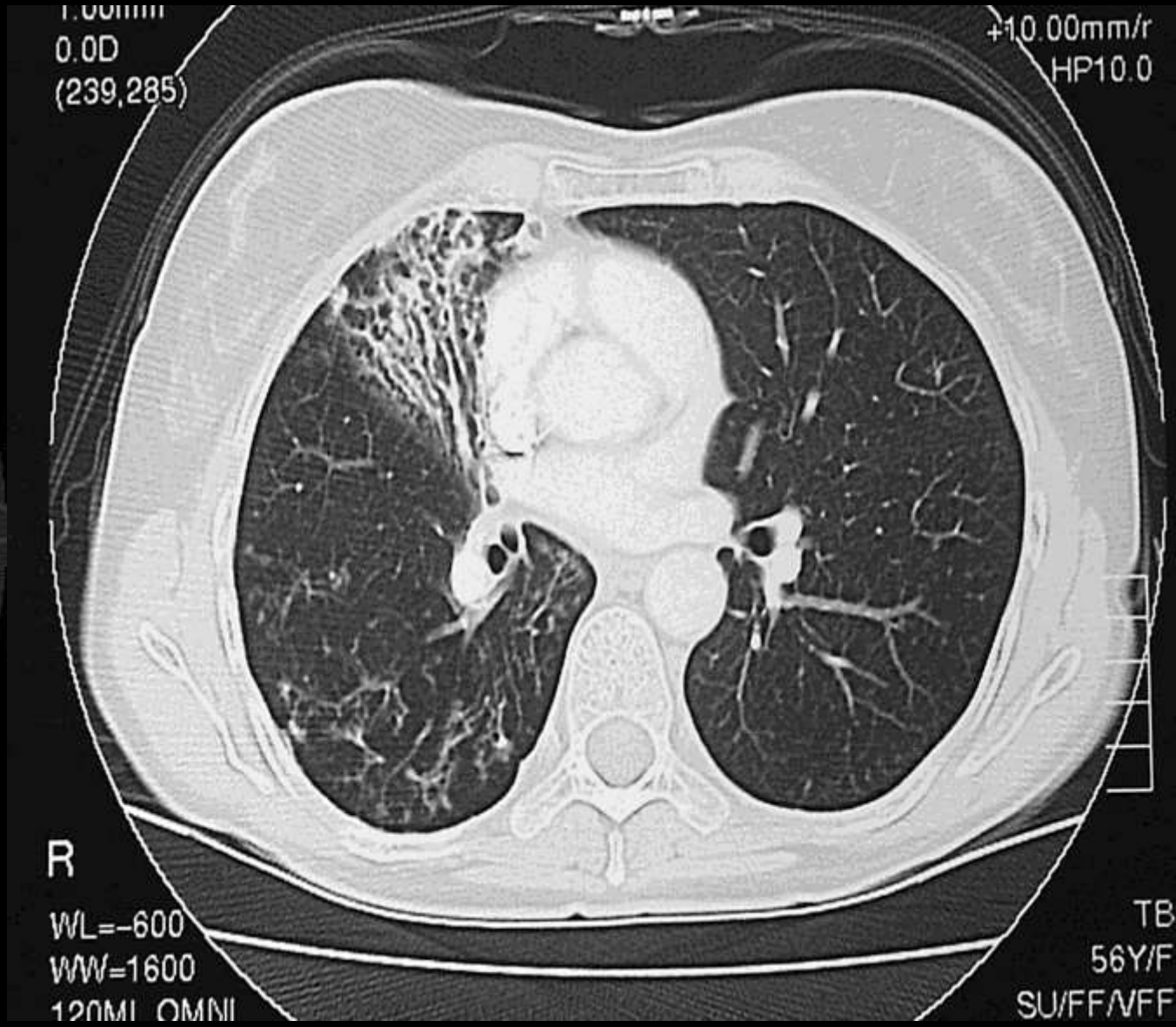

MAC

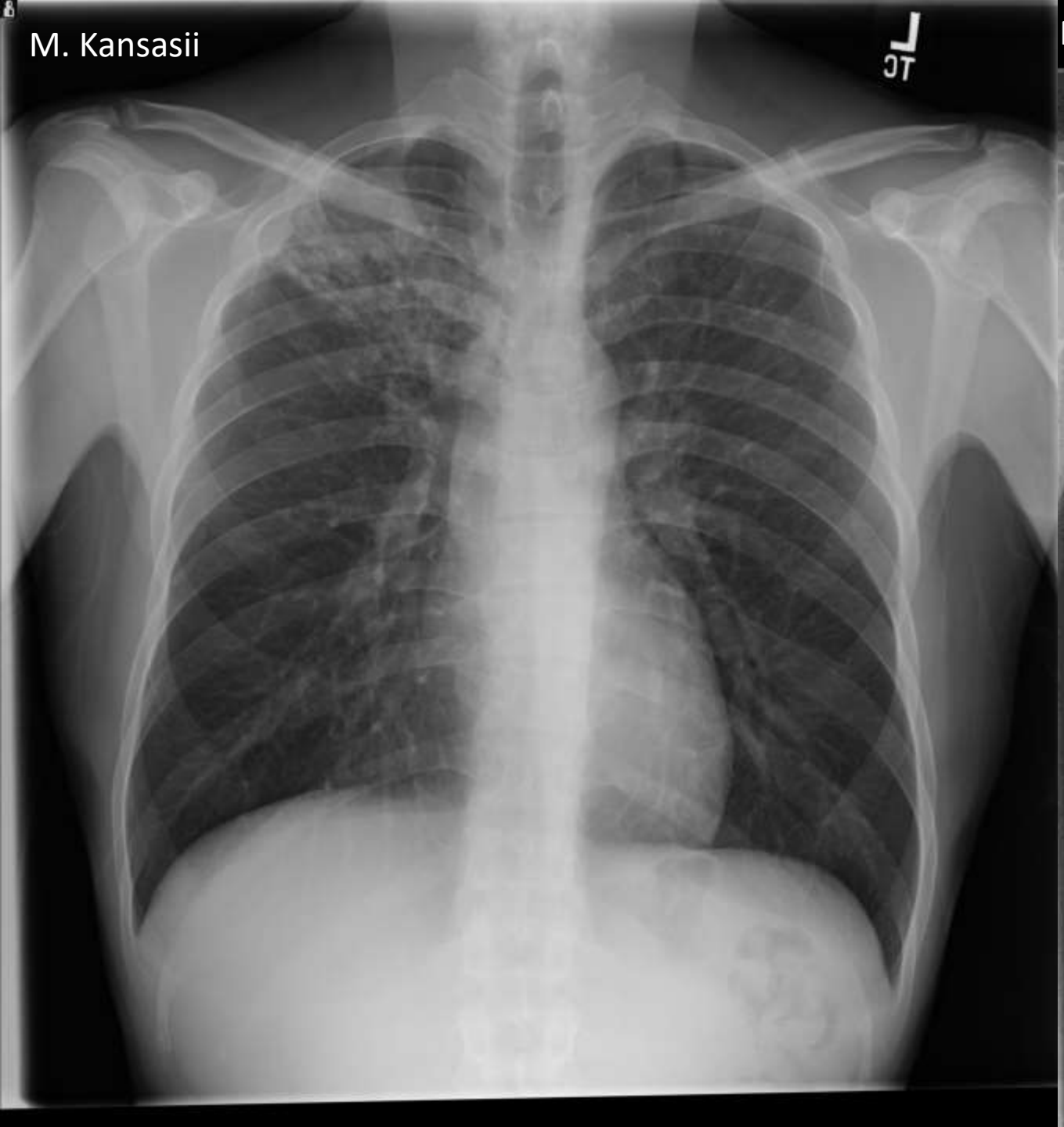

MAC

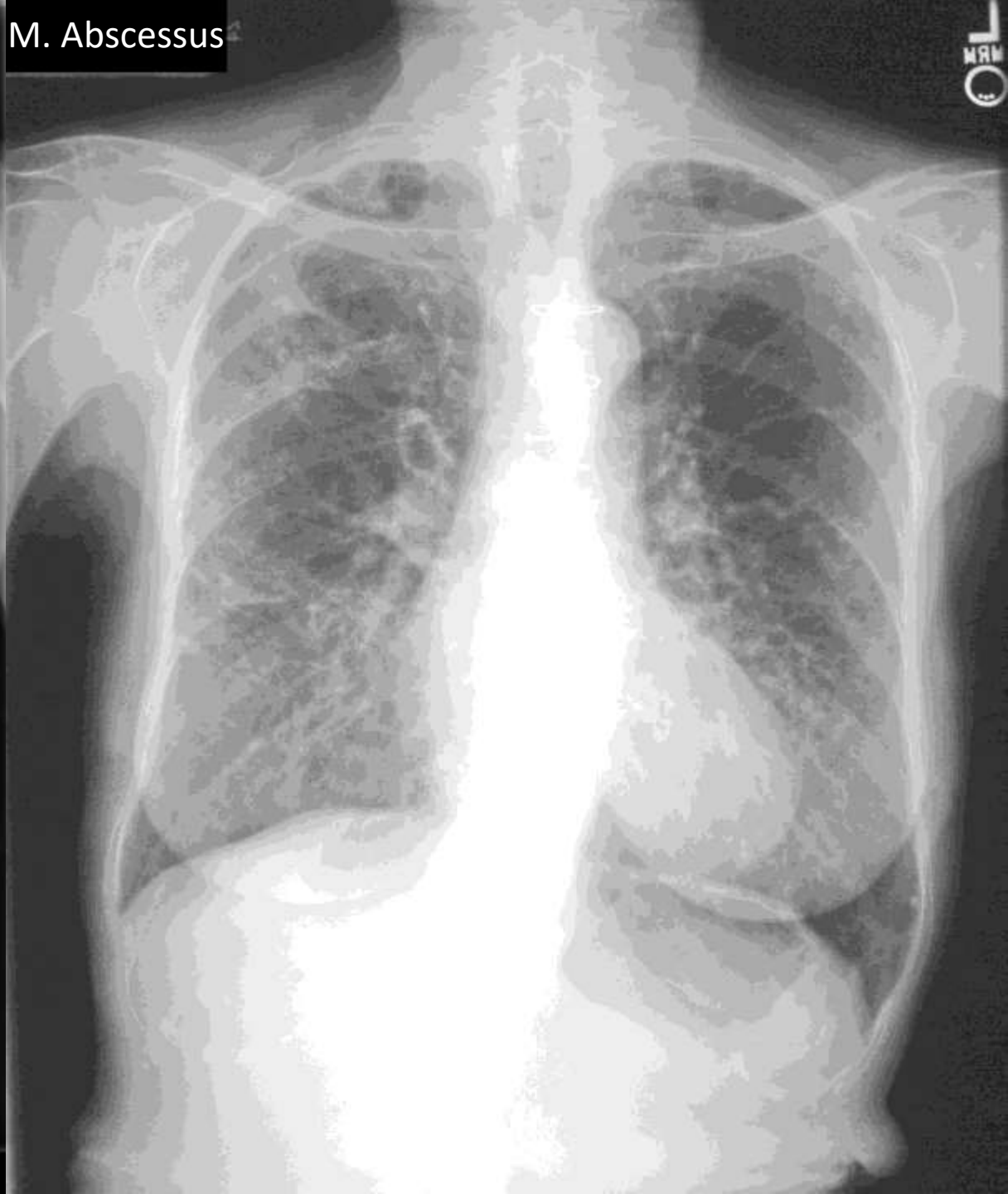
MAC



MAC




M. Kansasii


M. Abscessus

NTM pulmonary disease

Fibrocavitatory disease

- Commonly occurs in patients with COPD & other structural lung diseases including silicosis, pneumoconiosis or prior TB infections
- Often older males
- H/O of heavy smoking & heavy alcohol consumption
- Predominant symptoms
  - Productive cough (occurring in >80% of patients)
  - Weight loss or weakness (in approximately half)
  - Fever or night sweats (each in 10% to 20% of patients)

Am J Respir Crit Care Med 2007 Feb 15;175(4):367-416.

NTM pulmonary disease

Nodular/Bronchiectatic disease

- In middle-aged to elderly women with no preexisting lung disease
- Referred to as "the Lady Windermere syndrome"
- Presents with a more indolent clinical picture
- Usually present with chronic cough
- Mild scoliosis and pectus excavatum
- Chest radiograph may show discrete pulmonary nodules in middle lobe or lingular regions

Am J Respir Crit Care Med 2007 Feb 15;175(4):367-416.

NTM pulmonary disease

Hypersensitivity pneumonitis

- Known as "Hot-tub" lung disease
- Occurs in persons exposed to pools of heated water containing MAC
- Associated with standing water source, showers and aeration systems
- NTM are resistant to common disinfectants
- Common in metal working fluids (*M. immunogenum)*
- Young non smoker population

Am J Respir Crit Care Med 2007 Feb 15;175(4):367-416.

Hypersensitivity like disease

- Mild-to-moderate dyspnea
- Dry cough with or without fever
- Chest radiographs and CT scans :-
  - Centrilobular nodules
  - Ground-glass opacities
- MAC should be isolated form the respiratory specimens
- PFT can show mixed patterns
- Steroid with or without anti mycobacterial therapy

Radiology differences from Tuberculosis

NTM and TB	More common in TB	More common in NTM
Cavitary lesion or nodules	Thick walled cavity	Thin walled cavity
Multiple or single cavities	Cavity consolidation	Cavity & satellite nodules
Nodular infiltration	Bronchiectasis with upper lobe predominance.	Bronchiectasis with middle and upper lobe predominance
Tree-in-bud		

No imaging finding is sufficiently specific for diagnosis

Interlobular septal thickening	Unilateral disease
Consolidation	Randomly distributed nodules
Atelectasis	Calcified parenchyma
Lymphadenopathy	Calcified lymph node
Pleural calcification	Pleural effusion
	Pleural thickening

NTM and Cystic Fibrosis

- 10,000-fold greater prevalence in respiratory cultures from patients with CF
- Reported prevalence varies dramatically even at single centres
- Largest studies (US & Europe): overall prevalence is 6% to 13%
- Most common: MAC and *M.abscessus*
- Concept of colonization Vs indolent disease is an untested hypothesis
- One hypothesis is that Bronchiectasis in cyctic fibrosis is a resultant of NTM disease
- Yearly screening

Clin Chest Med 36 (2015) 101–115

Cystic fibrosis

- Other organisms should be considered and treated before initiating the therapy for NTM
- NTM should be ruled out before initiating macrolide monotherapy for CF
- Drug malabsorption due to pancreatic insufficiency adds to the enigma
- Surgical treatment should be reserved for severe, symptomatic and localized diseases
- NTM disease is not a concern in post transplant

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Specimen processing

- Samples from nonsterile body sites:
  - Decontamination by-NaLC-NaOH method (MC used)
- Sterile body sites-
  - Decontamination not required
- Tissues grounded aseptically in sterile physiological saline or bovine albumin & directly inoculated into media

Smear microscopy

- Screened by fluorochrome (auramine) staining
- Confirmed by ZN staining

Cultures

- Isolation of NTM is must for initiation of therapy
- Contamination of the specimen can be confounding factor
- Uncommon species are usually contaminants
- Three sputum samples on separate days
- All samples should have an AFB staining
- Bronchial washing samples- more sensitive and less prone to contamination
- Histopathological specimen with demonstration of GI and AFB is diagnostic
- GI on biopsy + negative Biopsy culture= should have BAL/sputum positive for diagnosis

Culture

ALL culture for NTM should include

SOLID	LIQUID	AUTOMATED
Lowenstein-Jensen agar	Middlebrook 7H9 broth	MGIT 960 (Becton-Dickinson)
Middlebrook 7H10 & 7H11		BACTEC 9000 MB
		VersaTREK (Trek Diagnostics)

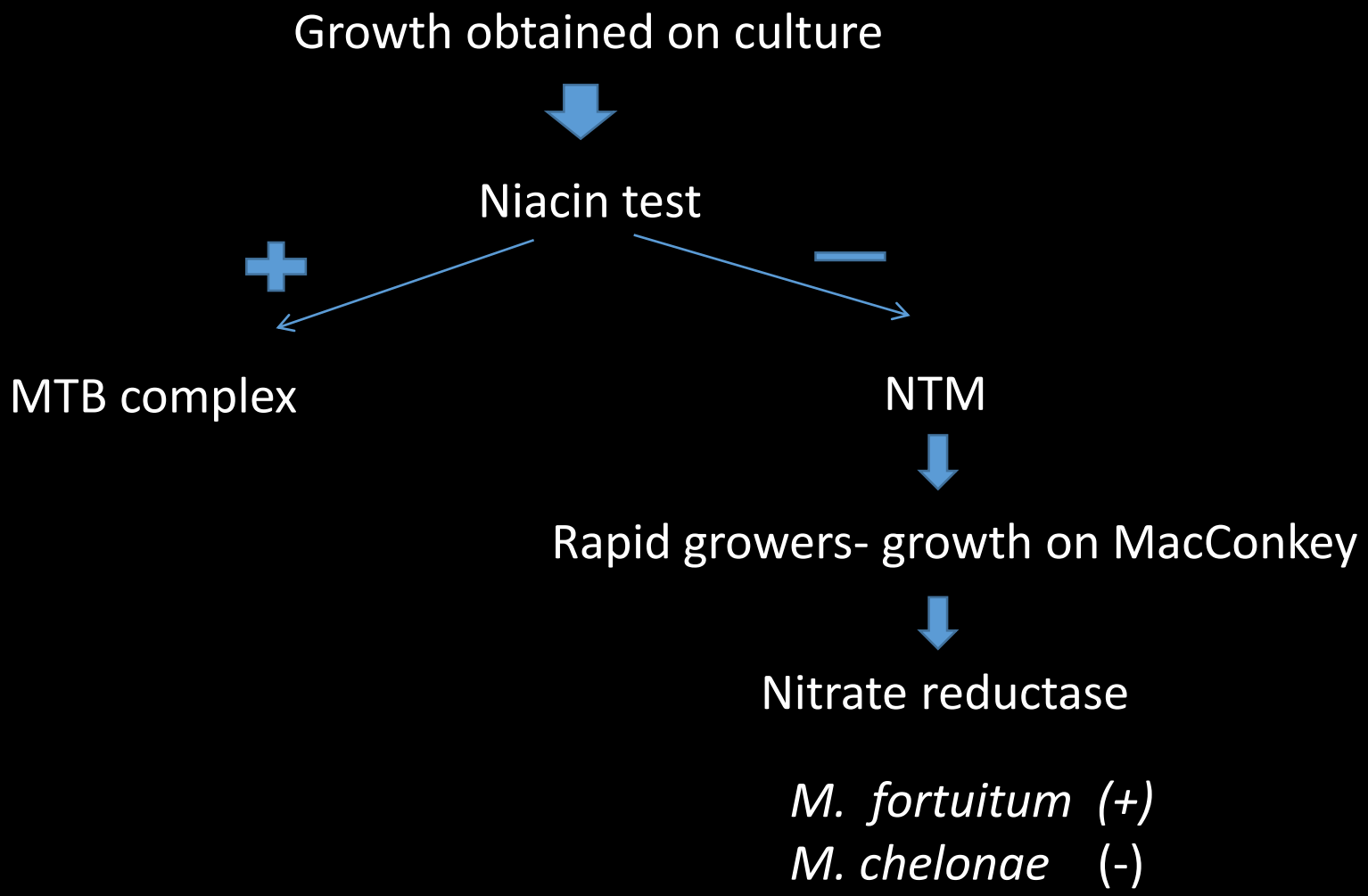
Special supplementation: *M. haemophilum* (Hemin)

Mycobacterium: General Characteristics, Laboratory Detection, and Staining Procedures. In: *Manual of Clinical Microbiology.* Canada: ASM, pp. 536-539.

NTM identification

- Phenotypic testing
- Biochemical Testing
- HPLC
- Mass spectrometry
- Nucleic acid based testing

Scheme for identification



Biochemical test

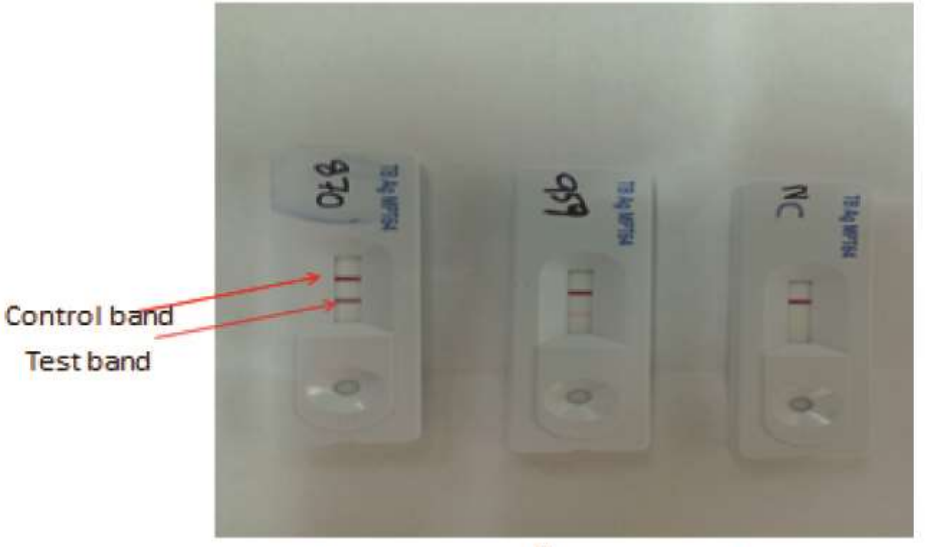
TEST	M.kansasii	M.marinum	M.simiae	M.asiaticum	MAC
Nitrate reduction	+	-	-	-	-
Catalase >45mm	+	v	+	+	-
Niacin	-	-/+	weak + (2-3%)	-	-
Arylsulfatase 2 wk	-/+	++	-/+	+/-	-
Urease	+	+	+/-	-	-

Chemotaxonomic Testing: HPLC

- Based on lipid composition analysis
- First saponification of mycobacterial cells
- Derivatization of mycolic acids to ester form
- Separation in columns and identification of patterns
- Highly sensitive and specific
- Limitation: time consuming and costly

MPT-64

- MPT64, a 24 kDa secretory protein one of the major antigens of MTb
- Simple and rapid Immunochromatographic test
- Using monoclonal anti-MPT64 antibody
- Able to discriminate between MTBC and NTM



Indian J Tuberc 2012; 59: 92-96

Molecular methods

- FDA approved: Acridium ester–labelled DNA probes specific for MAC, *M. kansasii*, and *M. gordonae*
- Currently used in many clinical laboratories (AccuProbe; Gen-Probe)
- Technique: based on release of target 16S rRNA from organism
- Identification of the species can be achieved within 2 hrs
- Specificity 100% Sensitivity 85 -100%

PRA (PCR restriction endonuclease assay)

- Based on coupling of PCR of a 441- bp sequence of gene *hsp65* followed by restriction enzyme digestion
- Size of restriction fragments are generally species specific
- Relatively rapid
- Do not require viable organisms
- Identifies many NTM species that are not identifiable phenotypically

Molecular typing methods

- Pulsed-field gel electrophoresis (PFGE)
- Involves embedding the isolates in agarose gels, lysing the DNA, and digesting chromosomal DNA with specific restriction endonucleases
- Time-consuming procedure

Final Diagnosis

- Other lung disease must be ruled out
- ATT can be started empirically till the evaluation is complete if AFB is positive
- Single set of criteria may be inaccurate
- Pure Colonization without disease is uncommon and should be evaluated for tissue invasion
- NTM is an indolent disease hence confirmed diagnosis should be made in all cases
- M. *Kansasii* is an exception due to its virulent nature (single positive specimen)
- Low virulence NTM isolation should be kept under follow up

Diagnosis

- Clinical symptoms
- Isolation of the NTM:
    - Sputum- at least 2 expectorated sputum samples should show growth
    - At least one BAL sample positive
    - Culture from biopsy specimen
- Histopathology: granulomatous inflammation with or without AFB positivity
- Chest X ray: Fibrocavitatory opacities
- HRCT chest: multifocal bronchiectasis with multiple nodules

Am J Respir Crit Care Med 2007 Feb 15;175(4):367-416.

ATS/IDSA 2007

TABLE 3. CLINICAL AND MICROBIOLOGIC CRITERIA FOR DIAGNOSING NONTUBERCULOUS MYCOBACTERIAL LUNG DISEASE*

Clinical (both required)

1. Pulmonary symptoms, nodular or cavitary opacities on chest radiograph, or a high-resolution computed tomography scan that shows multifocal bronchiectasis with multiple small nodules (A, I)*

and

2. Appropriate exclusion of other diagnoses (A, I)

Microbiologic

1. Positive culture results from at least two separate expectorated sputum samples (A, II). If the results from (1) are nondiagnostic, consider repeat sputum AFB smears and cultures (C, III).

or

2. Positive culture result from at least one bronchial wash or lavage (C, III)

or

3. Transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM (A, II)
4. Expert consultation should be obtained when NTM are recovered that are either infrequently encountered or that usually represent environmental contamination (C, III)
5. Patients who are suspected of having NTM lung disease but do not meet the diagnostic criteria should be followed until the diagnosis is firmly established or excluded (C, III)
6. 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 (C, III)

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Treatment

- Treatment duration: 12 to 24 months
- In vitro susceptibility might not correlate with in vivo effect
- Empiric therapy for NTM is not recommended
- Treatment is individualized as per pathogen
- Also in vitro DST is recommended for some species
- Drug toxicities also play role in decision making
- Immunosuppression changes treatment strategies.

Armentorium

- Macrolides
- Rifampicin
- Ethambutol
- Aminoglycosides
- Isoniazid
- Fluoroquinolones
- Surgery

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Mycobacterium Avium complex

Introduction

- Mycobacterium Avium: pulmonary disease and disseminated disease
- Mycobacterium intracellulare: pulmonary disease
- Found in water, soil, and in animals
- Most common NTM

MAC : Clinical Presentation

Fibrocavitatory disease

- Males
- Smokers
- Alcohol users
- Apical regions
- Progressively causing respiratory failure over 1 to 2 years

Nodular infiltrates

- Right middle lobe
- Postmenopausal
- Non smokers
- Lady Windermere syndrome
- Slower progression

MAC: Drug Treatment

- Macrolides: Clarithromycin > Azithromycin
- Only macrolide DST correlated with clinical response

Macrolide monotherapy (Wallace et al/Texas)

- Prospective, non comparative trial, low dose, daily, single drug study for non HIV MAC patients
- DST done: clarithromycin sensitive were included
- Dose: 500 mg BD
- Finally 80 pt were evaluated
- 79 pt showed culture response with 58 % becoming negative
- No control no follow up less no of patients. Non uniform population

Am J Respir Crit Care Med. 1994 May;149(5):1335-41

Azithromycin vs clarithromycin (Ward et al/Oregon)

- HIV positive
- Blood culture positive for MAC
- No previous treatment
- 600 mg azithromycin with 800 mg ethambutol vs 500mg BD clarithromycin with 800 mg ethambutol
- Follow up was done with blood cultures
- 59 subjects were enrolled

Clin Infect Dis. 1998 Nov;27(5):1278-85.

Results

- Study was stopped prematurely in view of interim analysis showing significant difference in culture negativity
- Clearance of bacteremia was 37 % in azithromycin arm and 87 % in the clarithromycin arm
- Clinical symptom improvement was not difference at per significance

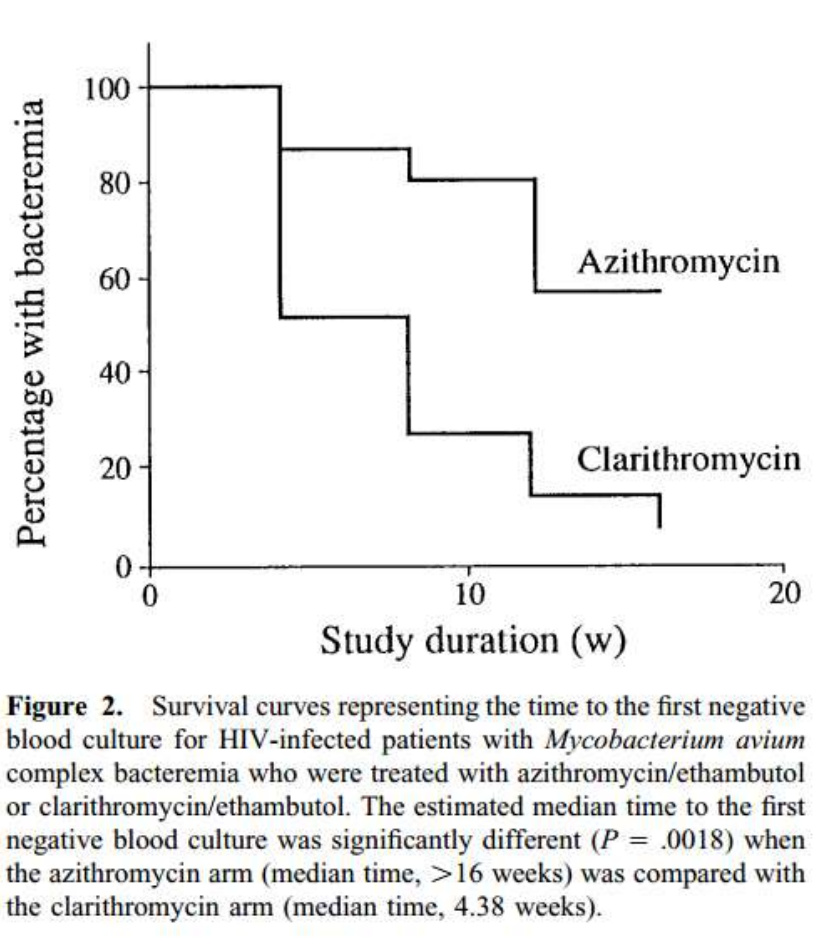


Figure 2. Survival curves representing the time to the first negative blood culture for HIV-infected patients with *Mycobacterium avium* complex bacteremia who were treated with azithromycin/ethambutol or clarithromycin/ethambutol. The estimated median time to the first negative blood culture was significantly different ($P = .0018$) when the azithromycin arm (median time, >16 weeks) was compared with the clarithromycin arm (median time, 4.38 weeks).

Clin Infect Dis. 1998 Nov;27(5):1278-85.

Azithromycin vs clarithromycin (Dunne et al/ Texas)

- Randomized controlled trial
- 246 HIV Positive pt with disseminated MAC
- US, Brazil, Argentina, Chile: 55 centers
- DST was done on all isolates
- Azithromycin 600 mg + Ethambutol Vs Clarithromycin 500mg BD + Ethambutol
- Duration for 24 weeks and follow up for one year

Clin Infect Dis. 2000 Nov;31(5):1245-52

Outcomes

	Azithromycin group	Clarithromycin group	p Value
Culture negativity	46%	56%	0.24
Relapses	39%	27%	0.21
Adverse effects	63%	66%	------
Clinical improvement at 12 weeks	68%	91%	0.02
Clinical improvement at 24 weeks	71%	73%	0.8

- Except for the early improvement in symptoms with clarithromycin group, the two drugs were similar

Intermittent therapy thrice weekly (Jeon et al/Seoul)

- Retrospective comparative
- Non HIV
- 8 year period
- Criteria used for diagnosis: 2007 ATS/IDSA
- Patient excluded:
  - Fibrocavitatory disease
  - Previous macrolide use in one month
  - Previous NTM treatment
  - High lever Clarithromycin resistance on DST
- Treated with rifampicin, ethambutol and oral macrolide

Am J Respir Crit Care Med. 2015 Jan 1;191(1):96-103

Dosage

	Daily	Intermittent
Clarithromycin/Azithromycin	1000/250	1000/500
Ethambutol	15mg/kg	25mg/kg
Rifampicin	600	600
Duration	24 Months	12 months of culture negativity (mean 18 months)

Outcomes

Table 4. Treatment Outcomes

	Daily Therapy (*n* = 99)	Intermittent Therapy (*n* = 118)	*P* Value
Improvement of symptom	74 (75%)	97 (82%)	0.181
Improvement of HRCT	67 (68%)	86 (73%)	0.402
Sputum culture conversion	75 (76%)	79 (67%)	0.154
Time of sputum culture conversion, d	34 (27–68)	35 (28–85)	0.149

Definition of abbreviation: HRCT = high-resolution computed tomography.

Risk factors for adverse response to intermittent therapy

- Old age
- AFB positivity
- Male

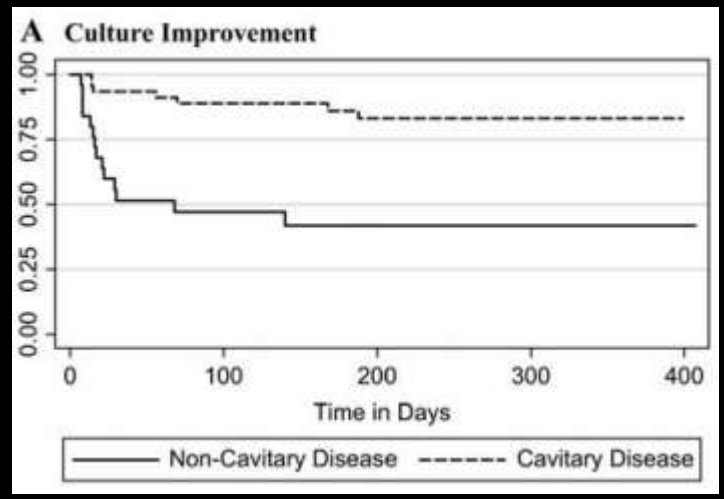
Factors predicting the success of intermittent regimen (Lam et al/San Diego)

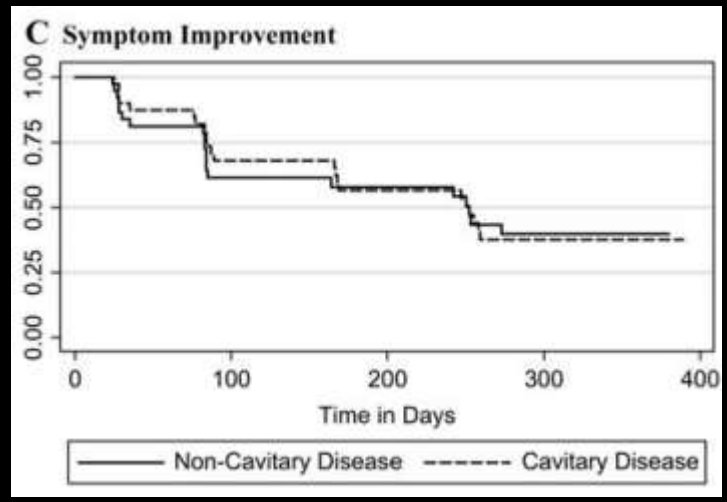
- Comparative, prospective trial
- Cavitatory vs non Cavitatory disease
- 91 HIV negative patients were treated with TIW regimen
- Followed up for one year with cultures

Am J Respir Crit Care Med.2006 Jun 1;173(11):1283-9

Outcomes

	Cavitatory	Non Cavitatory	Total
Culture negative	4.1	23.8	13.2
HRCT improved	46.2	77.3	60.4
Symptom improved	53.7	51.3	52.5





Am J Respir Crit Care Med.2006 Jun 1;173(11):1283-9

Discussion

- Non Cavitatory disease responded better than Cavitatory disease
- Older better than younger
- Previously non treated better than treated
- AFB negative responded well
- No history of COPD or bronchiectasis responded better
- HRCT response preceded symptom response and culture response

Am J Respir Crit Care Med.2006 Jun 1;173(11):1283-9

3 Vs 2 drug regimens (Miwa et al/Hamamatsu)

- Both types of MAC were included in the study
- 2007 ATS/IDSA criteria were used
- Immunosuppressed patients and clarithromycin resistant MAC population were excluded
- Treatment was given for 12 months
- Sputum conversion was defined as three sequential sputum culture to be negative

Ann Am Thorac Soc 2014 Jan;11(1):23-9

- Rationale: Rifampicin is the enzyme inducer hence decreasing the levels of clarithromycin (the most effective drug for MAC)
- Serum clarithromycin metabolite levels were estimated 2 weeks after the starting of treatment

Drugs	Dosage
Clarithromycin	600
Ethambutol	750
Rifampicin	450

Ann Am Thorac Soc 2014 Jan;11(1):23-9

Outcomes

- 2 drug regimen was not inferior to 3 drugs regimen
- 2 drug regimen should not be used in HIV positive and disseminated MAC infections
- Limitation: small population, no follow up as per recommendation, no continuation of treatment for 12 months

Ann Am Thorac Soc 2014 Jan;11(1):23-9

Use of fluoroquinolones (Fujita et al/Fukuoka)

- Rifampicin + ethambutol + gatifloxacin Vs Rifampicin + ethambutol + Clarithromycin
- Rationale: Gatifloxacin has a low MIC value on DST of MAC
- HIV/ Diabetic/ CHF were excluded
- End point was eradication defined as three sequential culture specimens to be negative
- Treatment given for one year
- 27 patients
- Adverse effects were more with gatifloxacin but insignificant

J Infect Chemother (2012) 18:146–151

Outcomes

- Relapse rates were similar
- Eradication rates were similar
- This study also demonstrated the clinical and MIC correlation (in vivo and in vitro)
- Limitations: small, observational, no long term follow up,
- Can be considered as second line
- Moxifloxacin, Satifloxacin also have lower MAC

J Infect Chemother (2012) 18:146–151

Role of aminoglycosides (Kobashi et al/Kurashiki)

- Streptomycin was used 15 mg /kg thrice weekly for three months
- Overall treatment constituted clarithromycin, ethambutol and rifampicin
- Duration of treatment was 24 months
- As per ATS IDSA guidelines 1997
- 146 patients were randomized
- Baseline clinical and demographical characteristics were matched
- HIV negative patients were included

Respiratory Medicine (2007) 101, 130–138

Outcomes

- Sputum conversion rates were statistically more in SM group
- No difference in sputum relapse rates
- No statistically significant difference was there w.r.t. clinical efficacy or radiological efficacy
- Also there were no statistically significant difference in adverse effects

Respiratory Medicine (2007) 101, 130–138

Role of interferon gamma (Virelles at al/Havana)

- Eighteen patients
- Rational: IFN gamma plays an important role in activation Th1 response and macrophages
- Patients with contraindication to interferon therapy were excluded
- IGN gamma was given daily for 4 weeks and thrice weekly for 20 weeks
- Conventional treatment that was given to both arms was ciprofloxacin, azithromycin, rifampicin and ethambutol
- Only 6 months treatment was given and 12 months follow up period

BMC Infect Dis. 2008 Feb 11;8:17.

Outcomes

- Radiological improvement was statistically more significant in the IFN group
- General clinical status was significantly better and improved early in the IFN group
- Adverse effects like flu like symptoms, cytopenias were well tolerated
- Response of MAC was better than that of M fortuitum and M. Kansasii

A word about HIV + MAC

- Prophylaxis : if CD4 < 50 cells/mm^3
- Drugs for prophylaxis: Clarithromycin > Azithromycin
- Drugs for treatment: Clarithromycin > Azithromycin + ethambutol ± Rifabutin
- Duration: 12 months after culture negativity
- ART: should be started after 2 weeks
- When to stop prophylaxis: CD4> 100 cells/mm^3 for 3 months

CDC 2015/ WHO 2014/ NACO 2007

Summarizing

- Clarithromycin DST is a must
- Monotherapy is not recommended
- Clarithromycin + Ethambutol + Rifabutin
- Azithromycin can be used in case of adverse effects
- TIW regimen can be used in patients without any risk factor for adverse outcome
- Aminoglycosides can be used for Cavitatory or disseminated disease
- Fluoroquinolones can used in second line

Mycobacterium kansasii

- Tap water is the most important source
- Second most common NTM in US
- Risk factor
    - HIV
    - Pneumoconiosis (silicosis)
    - COPD
    - Alcoholism
    - Malignancy
- Symptoms and clinical features are identical to M. Tb

Treatment

- ATT drugs: Ethambutol, Streptomycin and Rifampicin have actions against M. kansasii
- DST might not correlate with in vivo response
- Other drugs that are effective in vitro are: clarithromycin, amikacin, sulfamethoxazole, fluoroquinolones and rifabutin
- Rifampicin is the critical component of any regimen against M. kansasii
- DST shows that resistance to isoniazid and pyrazinamide is common

Drugs that have activity

Study	Observational lab based study by Diaz et all 2003/Spain	Comparative study of DST by Alcaidde et all Barcelona/2004
Participants	108 isolates of NTM were studied (8 isolates of M. kansasii)	148 isolated of consecutive clinical specimen were tested for susceptibility
Methods	DST of levofloxacin, moxifloxacin, gatifloxacin and linezolid were studied	Drugs used were INH, R, E, S, linezolid, Telithromycin, clarithromycin, levofloxacin and moxifloxacin
Result	All the drugs were active against M kansasii. Gatifloxacin and moxifloxacin having the lowest MIC	All were resistant to M tuberculosis doses of INH, R, S and E. In vitro activity of other drugs was moxifloxacin> levofloxacin=clarithromycin = linezolid >>> telithromycin

Int J Antimicrob Agents. 2003 Jun;21(6):585-8.
Antimicrob Agents Chemother. 2004 Dec;48(12):4562-5.

Era of Rifamycin

Study	Retrospective study, Banks et all (wales/1983)	Prospective study, Ahn et all (Texas/1983)
Participants	35 patient with diagnosis of M kansasii on multiple sputum cultures and symptomatic disease were reviewed	40 patients were included, diagnosis was made on Chest X ray findings of cavitation and multiple sputum cultures to be positive
Methods	Cure was defined on the discretion of treating physician, repeated culture negativity and radiographic improvement. All regimens had rifampicin and ethambutol	Treated with R, INH, E for 12 months, and streptomycin 1gm twice weekly for 3 months
Result	66% had preexisting lung disease, 88% were smokers, all sputum samples were sensitive for Rifampicin, 90% had Cavitatory disease, 5 died during study, 100 % sputum conversion, no relapse for 5 ½ years	70 % had underlying lung disease, after 12 months of chemotherapy and mean 31 months of follow up there was one relapse at 6 months. Culture negativity was achieved at mean on 5.5 weeks

Thorax 1983 Apr; 38(4): 271–274.
Am Rev Respir Dis 1983 Dec;128(6):1048-50.

Standardization of regimens

Study	Retrospective study by Ahn et all (Texas/1981)	Prospective multicentric by Jenkins et all (BTS/Cardiff/ 1994)
Participants	Evaluation of chemotherapy of 256 patient with M. kansasii	173 patients with M. Kansasii in multiple sputum culture with Cavitatory disease on CXR were recruited
Methods	Records, cultures and DST were reviewed	Given rifampicin and ethambutol for 9 months and followed up for 51 months
Result	Of regimens containing rifampicin 100% had sputum conversion at 4 months with none relapsing, but of regimens not containing rifampicin 90% had sputum conversion at 4 months with 7 % relapsing Duration of chemotherapy course was not analyzed.	50 % had pervious history of lung disease, 9 % relapsed, one patients never had culture negativity, radiographic improvement was noticed in 80%. 15 died during study (8 of respiratory failure only one of whom was having culture positivity)

Thorax. 1994 May; 49(5): 442–445.
Rev Infect Dis. 1981 Sep-Oct;3(5):1028-34.

R + E + M

Study	Prospective uncontrolled study by Griffith et all 2003/Texas
Participants	18 consecutive patients of M Kansasii lung disease (non pregnant, non HIV, no history of life threatening disease, no resistance to R or macrolides)
Methods	Sputum samples were obtained monthly, pretreatment DST to R and clarithromycin was done. All patients received clarithromycin 500/1000mg, R 600mg, ethambutol 25 mg/kg thrice weekly. Therapeutic end point was 12 months of culture negativity
Result	13 pt had bilateral upper lobe cavities, rest had nodulo-bronchiectatic disease. Time to sputum conversion was 1 ± 0.9 months. Duration of therapy 13.4 ± 0.9 months. No pt had relapsed after 4 years of follow up.

Clin Infect Dis. 2003 Nov 1;37(9):1178-82.

Summarizing

- Highly virulent disease
- Presentation is similar to M. Tuberculosis
- Rifampicin is the most active drug
- Rifampicin DST should be done
- R, E, M and Streptomycin are active drugs

Mycobacterium abscessus

Clinical characteristics

- Nodular bronchiectasis is the main manifestation of M. Abscessus group lung disease
- Most common radiological feature is multiple micro-nodules, bronchiectasis, tree in bud.
- M. abscessus is the most common RGM
- Recently M Abscessus has been differentiated into M. abscessus sensu stricto, M. massiliense, and M. bolletii
- Treatment responses are better for M. massiliense compared to M Abscessus

Zhonghua Jie He He Hu Xi Za Zhi. 2013 Sep;36(9):671-4.
Radiology. 2012 Apr;263(1):260-70.

RGM introduction

Study	Retrospective study by Griffith et all (Texas/1993)
Participants/Methods	154 clinical isolates of RGM were identified who fulfilled ATS diagnostic criteria
Result	Predominant patients were white, female, non smokers Upper lobe infiltrates was the most common radiographic feature (88%)with 77% having bilateral disease Only 16% had cavities 8% had coexistent MAC isolation 82% were M abscessus and rest were M fortuitum 14 % died as a consequence of respiratory failure attributable to RGM
Conclusion	Fortuitum isolate showed better response to antibiotic and M abscessus had better response to surgery

Am Rev Respir Dis. 1993 May;147(5):1271-8.

Non Human studies

Study	Comparative lab based experimental study by Choi et all (Daejeon, Korea/ 2012)
Participants	23 M. abscessus and 24 M. massiliense isolates were studies and followed up
Methods	Clarithromycin and azithromycin sensitivity Was tested along with erm41 gene testing and gene knockout,
Result	Clarithromycin has lower MIC for M abscessus as well as M Massiliense Inducible resistance is more common in clarithromycin than azithromycin Clarithromycin induces *erm* gene more than azithromycin In lung model Azithromycin had significantly more decrease in bacterial load as compared to clarithromycin Serum and lung level distribution was equal for CLR and AZM
Conclusion	Azithromycin has lower resistance rates against M Abscessus but response is equal in M Massiliense

Am J Respir Crit Care Med. 2012 Nov 1;186(9):917-25.

Preliminary studies

Study	Retrospective study by Huang et all (Taiwan/2010)
Participants/Methods	40 pt records who were diagnosed with M. abscessus were reviewed and with performing DST
Result	Only 22 pt met with the criteria of M. Abscessus pulmonary disease Cough, fever, hemoptysis were the most common symptoms Radiographically retico-nodular opacities, consolidation and cavities were most common All isolates were sensitive to antibiotics (full spectrum) Treatment failure by the end of 12th month was 27%
Conclusion	M Abscessus is naturally sensitive to clarithromycin and amikacin Variably sensitive to cefoxitin and amikacin Therapy require prolonged course with parenteral antibiotics Relapse rates are still high

J Microbiol Immunol Infect. 2010 Oct;43(5):401-6

One Parenteral Vs two Parenteral

Study	Retrospective study by Lyu et all (South Korea/ 2012)
Participants/Methods	41 Pt treated as per ATS guidelines for M abscessus were reviewed and follow up were taken
Result	41 pt were treated with macrolide and one parenteral drug 58 % were treated with macrolides and two parenteral drugs Mean duration of parenteral drugs was 230 days and mean duration for total treatment was 511 days Treatment success, failure and relapse rate s were 80.5, 12.2, 7.3 % There was no significant difference between those receiving two or one parenteral drugs
Conclusion	Combination antibiotic therapy, including long-term (minimum 2–4 months) parenteral drugs, as recommended by the ATS, resulted in successful treatment outcomes in 80.5% of patients with *M. abscessus* lung disease in Korea.

Respir Med. 2011 May;105(5):781-7

Differentiation into subspecies

Study	Retrospective study by Koh et all (Seol/ 2011)
Participants/Methods	Molecular identification , along with comparison of clinical profile and treatment outcome were compared for 64 pt of M. abscessus and 81 pt M. Massiliense
Result	Clinical characteristics and radiographic abnormalities were similar in both groups Most of the pt in both groups received clarithromycin along with one month of parenteral cefoxitin and amikacin Sputum conversion and maintenance of negative sputum was 88 % in M. massiliense and 27% in M. abscessus All clinical isolates of M Abscessus had clarithromycin inducible resistance
Conclusion	Treatment responses are higher in M Massiliense Inducible in vivo resistance might explain the lack of response in M. abscessus

Am J Respir Crit Care Med. 2011 Feb 1;183(3):405-10.

M. Abscessus and its subspecies

Study	Retrospective study by Harada et all (Sapporo/ 2013)
Participants/Methods	Molecular identification, clinical characteristic, treatment outcome comparison was done for 102 RGM isolates was done 72 were M Abscessus, 27 M Massiliense, 3 M Bollete
Result	Clinical characteristics were similar Among radiologic features bronchiectasis was significantly more common in M abscessus than other but rest of the findings were similar Streptomycin was uniformly ineffective, imipenem resistance was more in M. massiliense as compared to M abscessus All ATT were ineffective as were ciprofloxacin and moxifloxacin Sputum conversion rates were lower for M abscessus and relapse rates were higher
Conclusion	Treatment responses rates with CAM-based antibiotic therapy were higher for *M. massiliense* than in *M. abscessus* lung disease

J Clin Microbiol. 2012 Nov;50(11):3556-61

M. Abscessus Vs M. Massiliense

Study	Retrospective study to compare the clinical outcomes of M Abscessus and M massiliense by Lyu et all (South Korea/2014)
Participants/Methods	59 pt with M. abscessus and 69 with M. massiliense were reviewed for treatment outcomes
Result	Most common regimen was Macrolide + amikacin + cefoxitin followed by M + A+ Imipenem Treatment duration for parenteral drugs was 7.4 month for M. Abscessus and 4.7 months for M Massiliense Total treatment duration was 16 months for M. Abscessus and 12.1 months for M Massiliense Relapse rate was 19% in M. massiliense and 27% in M. abscessus
Conclusion	Patients with M. massiliense pulmonary infection responded better to this antibiotic strategy than those with M. abscessus infection.

Respir Med. 2014 Nov;108(11):1706-12.

In Cystic Fibrosis

Study	Prospective cohort study by Roux et all (Guyancourt France/ 2015)
Participants/Methods	16 pt with M Massiliense and 27 with M abscessus lung infection along with cystic fibrosis were followed up for 6 years
Result	M. Massiliense pt were significantly younger and had lower BMI as compared to the pt with M abscessus Transient colonization was more common with M. massiliense, eradication with antibiotic therapy was early and more prolonged with M. massiliense
Conclusion	Particular link between M. massiliense and malnutrition specifically in CF patients Antibiotic response is better with M. massiliense

J Cyst Fibros. 2015 Jan;14(1):63-9

Newer therapies

Study	Retrospective analysis of Tigecycline containing regimens for M. Abscessus by Wallace (Texas/2014)	Retrospective analysis of inhaled Amikacin for mycobacterium abscessus by Olivier (Boston/ 2013)
Participants	52 patient records were reviewed	Records reviewed from 2003 to 2010
Methods	Patients were reviewed on the basis of length of Tigecycline use	Inhaled amikacin (n=20) Amikacin 250mg/ml was nebulized with 3 ml saline and was started at OD dose was titrated every 2 weekly to 500mg BD
Result	88 %had already received macrolide, amikacin and linezolid, 69% had pulmonary disease 58 %had underlying cystic fibrosis 61 % were considered improved.	9 had Cavitatory lung disease, mean duration of treatment was 60 months before Amikacin. Followed up for median of 19 months. 45 % showed improvement is symptoms and 25 %had persistent culture negativity. 35% required Amikacin discontinuance in view of adverse effects.
Conclusion	With the use of Tigecycline for M. abscessus for more than one month 60% patients result in improvement and 90% will have adverse effects	Inhaled amikacin can be considered as salvage treatment in refractory cases of M. Abscessus

J Antimiroc Chemother. 2014 Jul;69(7):1945-53
Ann Am Thorac Soc. 2014 Jan;11(1):30-5

Surgery (for NTM)

Study	Retrospective analysis of pneumectomies for NTM by Shiraishi et all (Tokyo/2004)
Participants	53 patients infected with nontuberculous mycobacteria underwent 55 pulmonary resections
Methods	Indications for pneumonectomy included multiple cavities in one lung and destruction of an entire lung. Predominant disease was MAC and M. abscessus
Result	No operative mortality, 3 pt developed BP fistula, two late deaths, No relapse, symptoms improvement in all
Conclusion	Despite bronchial stump protection, right pneumonectomy carries a risk for bronchopleural fistula. Nonetheless, pneumonectomy can result in high cure rates in patients with nontuberculous mycobacterial infections.

Ann Thorac Surg. 2004 Aug;78(2):399-403.

Surgery for M. Abscessus

Study	Retrospective analysis of medical Vs surgical management in M abscessus by Jarand et all (Colorado/2010)
Participants	69 patients of known M abscessus pulmonary disease were reviewed
Methods	Routine follow up data was collected apart from review of culture records
Result	23 underwent surgery in addition to medical treatment and 46 received only medical treatment. 98% had nodulo-bronchiectatic disease and 44% had cavities. 92 % had bilateral multilobar disease Most common antibiotics given were Azithromycin, amikacin, imipenem, Clarithromycin, cefoxitin, ciprofloxacin. 25 lobectomies and 6 pneumectomies 39% became sputum negative in medical arm and 65 % in surgical arm 61% and 35% in medical arm and surgical arm respectively either never converted or relapsed
Conclusion	Surgical resection offers a prolonged microbiologic response

Clin Infect Dis. 2011 Mar 1;52(5):565-71

Summarizing

- No antibiotic regimen has been proven to be superior to other
- Most of the effective antibiotics are parenteral except macrolides
- Commonly effective parenteral antibiotics are amikacin, imipenem, cefoxitin
- Newer antibiotics found to have in vitro activity but not studied are: linezolid, Tigecycline, Telithromycin
- Surgery is the only curative option for pt with limited disease
- Surgery should be early unlike in other NTM species

Kekkaku. 2015 Mar;90(3):407-13.
Clin Chest Med. 2015 Mar;36(1):67-78

Mycobacterium Fortuitum

Introduction

- RGM
- Pulmonary disease similar to M. Abscessus (though less common)
- Exception: pt with GERD and chronic vomitings with RGM pulmonary disease both occur in equal frequency
- Susceptible to most of the drugs
- erm38 gene is present- responsible for the inducible macrolide resistance
- Commonly found in heavy metal industries

J Antimicrob Chemo. (2005) 55, 170–177
Antimicrob Agents Chemother. 1984 Oct;26(4):594-6.

RGM introduction

Study	Retrospective study by Griffith et all (Texas/1993)
Participants/Methods	154 clinical isolates of RGM were identified who fulfilled ATS diagnostic criteria
Result	Predominant patients were white, female, non smokers Upper lobe infiltrates was the most common radiographic feature (88%)with 77% having bilateral disease Only 16% had cavities 8% had coexistent MAC isolation 82% were M abscessus and rest were M fortuitum 14 % died as a consequence of respiratory failure attributable to RGM
Conclusion	***Fortuitum isolate showed better response to antibiotic*** and M abscessus had better response to surgery

Am Rev Respir Dis. 1993 May;147(5):1271-8.

DST studies

Study	Laboratory based study for DST to various drugs in M Fortuitum by Swenson et all (Texas/1985)
Participants/Methods	258 clinical isolates were tested for susceptibility with Broth microdilution test against Amikacin, Cefoxitin, Tobramycin, Doxycycline, Erythromycin & Ciprofloxacin
Result	DST to Amikacin, Cefoxitin showed susceptibility Uniformly resistant to erythromycin Variable resistant to Doxycycline and ciprofloxacin
Conclusion	In vitro susceptibility test should be performed for all clinical isolates of M. Fortuitum

Antimicrob Agents Chemother. 1985 Dec;28(6):807-11.

Summarizing

- Second most common RGM
- Lack of studies for standardization of protocols
- DST shows that most of the drugs are active
- M + R + E seems reasonable option

Finally…

Lack of adherence to the guidelines (Adjemian et al/Bethesda)

- 582 NTM treating physicians were contacted with a questionnaire
- Along with treatment record extracted for last 4 NTM patient they treated
- This data was compared with ATS/IDSA 2007 guidelines

Ann Am Thorac Soc. 2014 Jan; 11(1): 9–16.

Result

- 13 % antibiotic regimens met the criteria of ATS/IDSA
- 56 % did not contain a macrolide
- 16 % had macrolide monotherapy
- For M. *abscessus* 64 % did not contain macrolide
- Among Pulmonologists the adherence to the guidelines was 18%

Table 3. Antibiotic regimens prescribed to patients treated for *Mycobacterium avium* complex by physician specialty

Treatment Regimen	Regimens Prescribed to Patients with MAC by Treating Physician Specialty		
	Infectious Disease *n* (%)	Pulmonology *n* (%)	Family/General Practice and Internal Medicine *n* (%)
Total number of regimens prescribed (mean # regimens per patient)	194 (1.5)	237 (2.0)	88 (1.5)
Treatment regimens meeting ATS/IDSA guidelines	20 (10)	42 (18)	8 (9)
Macrolide, ethambutol, and rifamycin	19 (10)	41 (17)	8 (9)
Macrolide, ethambutol, rifamycin, and parenteral aminoglycoside	1 (0.5)	1 (0.4)	—
Treatment regimens not meeting ATS/IDSA guidelines for MAC*	174 (90)	195 (82)	80 (91)
Treatment regimens that may increase macrolide resistance	45 (23)	95 (40)	20 (23)
Macrolide monotherapy	23 (12)	51 (22)	10 (11)
Macrolide plus fluoroquinolone	4 (2)	3 (1)	1 (1)
Macrolide plus rifampin	18 (9)	41 (17)	9 (10)
Treatment regiments that are of unknown clinical significance	3 (2)	—	—
Macrolide plus inhaled amikacin	1 (0.5)	—	—
Macrolide plus linezolid	2 (1)	—	—
Treatment regimens that do not include macrolides	126 (65)	100 (42)	60 (68)
Ethambutol plus rifamycin	35 (18)	53 (22)	17 (19)
Fluoroquinolone based regimen	44 (23)	25 (11)	13 (15)
Parenteral aminoglycoside based regimen	1 (0.5)	1 (0.4)	10 (11)
Linezolid based regimen	1 (0.5)	—	—
Any nonmacrolide antibiotic monotherapy regimen	45 (23)	21 (9)	20 (23)