BSc Paediatric Infectious Diseases module

16/01/12

Non-Tuberculous Mycobacteria (NTM)

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Questions to consider

- What are non-tuberculous mycobacteria (as opposed to *M. tuberculosis*)?
- What are the clinical manifestations of NTM infection -> disease?
- How do I define the difference between NTM infection and disease?
- Actually, who suffers from NTM disease?
- What are the current diagnostic recommendations?
- How well established are our therapeutic regimens?
- What research does still need to be done?

American Thoracic Society Documents

An Official ATS/IDSA Statement: Diagnosis, Treatment, and Prevention of Nontuberculous Mycobacterial Diseases

David E. Griffith, Timothy Aksamit, Barbara A. Brown-Elliott, Antonino Catanzaro, Charles Daley, Fred Gordin, Steven M. Holland, Robert Horsburgh, Gwen Huitt, Michael F. Iademarco, Michael Iseman, Kenneth Olivier, Stephen Ruoss, C. Fordham von Reyn, Richard J. Wallace, Jr., and Kevin Winthrop, on behalf of the ATS Mycobacterial Diseases Subcommittee

This Official Statement of the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) was adopted by the ATS Board Of Directors, September 2006, and by the IDSA Board of Directors, January 2007

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Am J Respir Crit Care Med 2007;175:367-416 (50 pages!)

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NTM species

- *M. avium* Complex
- *M. kansasii*
- *M. abscessus*
- *M. chelonae*
- *M. fortuitum*
- *M. genavense*
- *M. gordonae*
- *M. haemophilum*
- *M. immunogenum*
- *M. malmoense*
- *M. marinum*
- *M. mucogenicum*
- *M. nonchromogenicum*
- *M. scrofolaceum*
- *M. simiae*
- *M. smegmatis*
- *M. szulgai*
- *M. terrae complex*
- *M. ulcerans*
- *M. xenopi*
- ..... → > >140 Species

  (1997: 50 species!)

http://www.bacterio.cict.fr/m/mycobacterium.html

Epidemiology

- Environmental reservoir: soil, lakes, rivers und tap water..
  Specific source of infection still unclear...
- NO transmission animal → human or human → human
- can lead to either asymptomatic infection or symptomatic disease
- NO latent infection → NO reactivation
- Incidence: only little information, estimated: 1.0 – 1.8 per 100‘000 (U.S.)
- Most common: MAC (*M. avium* Complex) > *M. fortuitum* > *M. kansasii*
- NTM > *M. tuberculosis*
- Lungs (75%) > disseminated disease (5%) > Skin/soft tissue (2%) > LN (0.4%)

Epidemiology

- Generally 2 types of pulmonary disease:
  - Classical: patients with NTM disease often secondary to underlying lung disease (COPD, prior TB infection, or interstitial lung disease).
    radiographically indistinguishable from TB:
    nodular opacities in the apices, cavitation, apical pleural thickening, and bronchogenic spread
  - Non-classical: characterized by a haphazard distribution of **multiple bilateral nodular and irregular interstitial opacities** (<1 cm).
    Not necessarily related to any underlying chronic lung disease and is found most often in women

Pathogenesis

- **HIV-Patients**

  Disseminated disease when CD4-count < 50/µl

- **Non-HIV-Patients**

  Some genetic syndromes associated with disseminated disease

  → IFN-γ und IL-12 pathways

  ! On treatment withTNFα-inhibitors (i.e. Infliximab)

  ! Organ transplant recipients (solid, BMT)

- **Some known clinical associations**

  Bronchiectasis, COPD, Pneumoconiosis, alveolar proteinosis, CF,

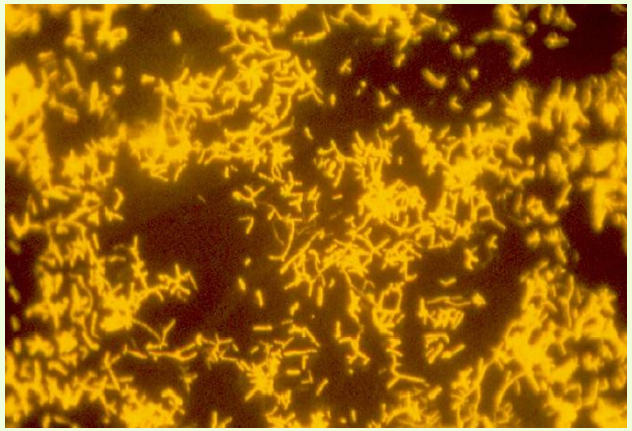
  α_1-AT-deficiency, previous pulmonary tuberculosis,

  oesophageal dysmotility.

  Nodular/bronchiectatic MAC disease is associated with postmenopausale women + characteristic habitus (Bronchiectasis + Pectus excavatum + scoliosis + mitral valve prolaps)

Lab diagnostics
Resistance testing

Laboratory investigation



- No fixation of original probe
- Special blood culture bottles
  NOTE: RGM do grow in conventional blood culture bottles
  (Rapid Growing Mycobacteria: *M. fortuitum, M. abscessus, M. chelonae*)
- Fluorescence microscopy is more sensitive than Ziehl-Neelsen staining
- All cultures should include solid and broth (liquid) media for detection and enhancement of growth.
  NOTE: - some species require lower incubation temperatures,
  - some other species need special supplements (fastidious NTM)
  Growth usually after 2-3 weeks, RGM *per definitionem* within 7 days.
- All clinically significant NTM isolates should be identified to the species level (Chromatography), PCR, 16S rRNA-Sequencing). Identifying MAC suffices.

Resistance testing - recommendations

- Routine-resistance testing of MAC isolates to determine Clarithromycin MIC.
  (untreated strains usually 4ug/ml; after treatment inevitably >32 ug/ml)

- Routine-resistance testing of *M. kansasii* for Rifampicin
  (as treatment failure is usually associated with RMP resistance).
  In case of RMP resistance: additional testing for Rifabutin, Ethambutol, Isoniazid, Clarithromycin, Fluoroquinolone, Amikacin und Sulfonamide

- RGM (Rapid Growing Mycobacteria: *M. fortuitum, M. abscessus, M. chelonae*) should all be tested for Amikacin, Imipenem, Doxycycline, Fluoroquinolones, Trimethoprim-Sulfomethoxazol, Cefoxitine, Clarithromycine, Linezolid and Tobramycine.

1 Pulmonary NTM disease

2 Disseminated NTM disease

3 Lymphatic NTM disease

4 Skin, Soft tissue and skeletal NTM disease

1 Pulmonary NTM-disease

- **Epidemiology**

  MAC > *M. kansasii* > *M. abscessus* (RGM)

  Patients > 50 Jahre (mean age 57 years), male>female

  (but: more recent studies suggest a postmenopausal female patients predominance for MAC lung disease)

- **Clinical symptoms**

  unspecific: chronic cough, dyspnoea, haemoptysis

  unspecific systemic symptoms

  (often difficult to differentiate due to symptoms of underlying lung disease)

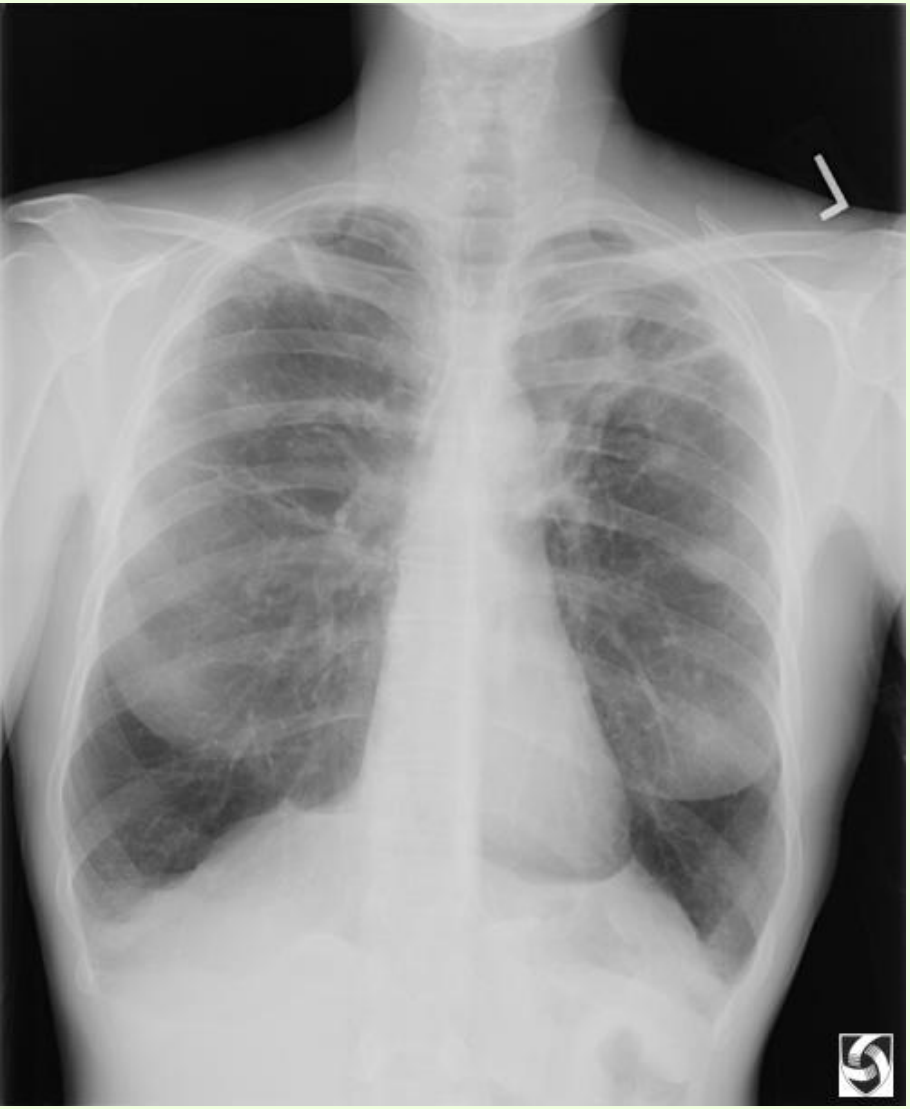
- **Radiological findings**

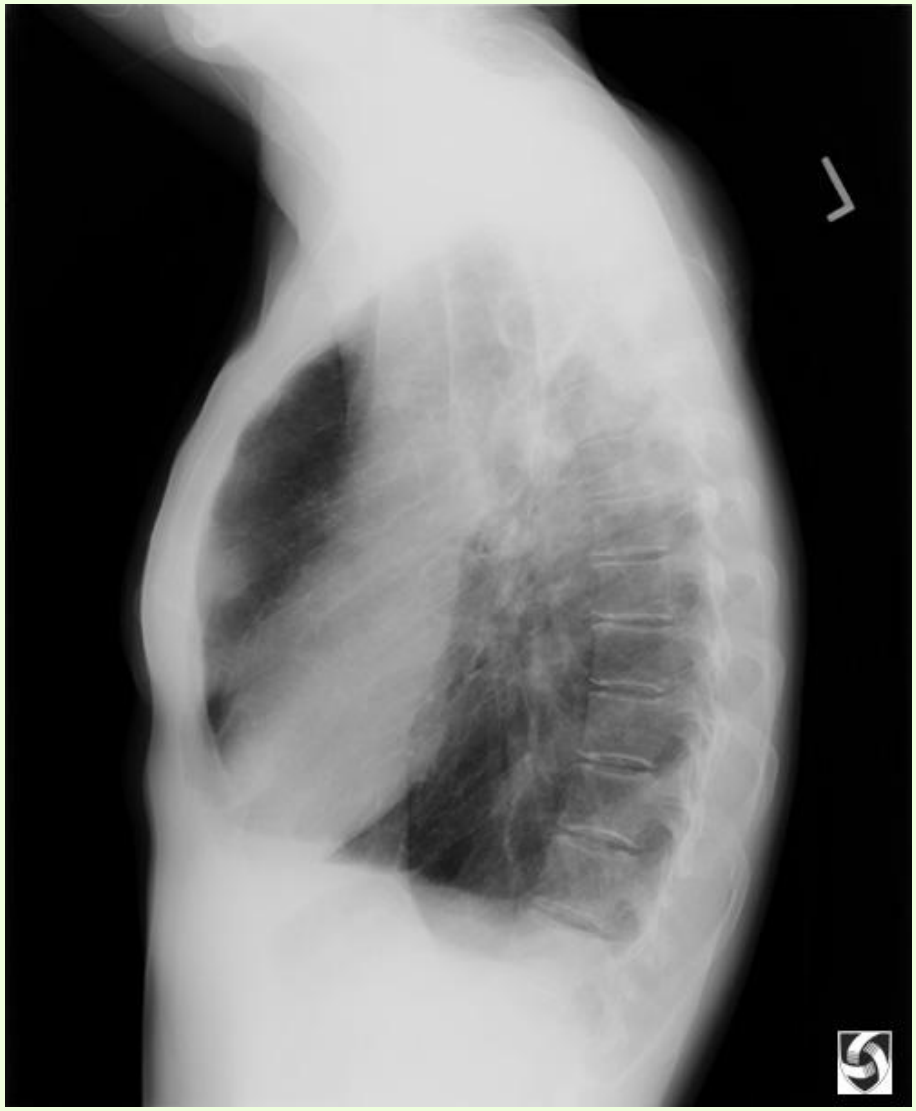
  mainly **fibro-cavitary** (CXR) or **nodular/bronchiectatic** (HRCT)

A clinical case

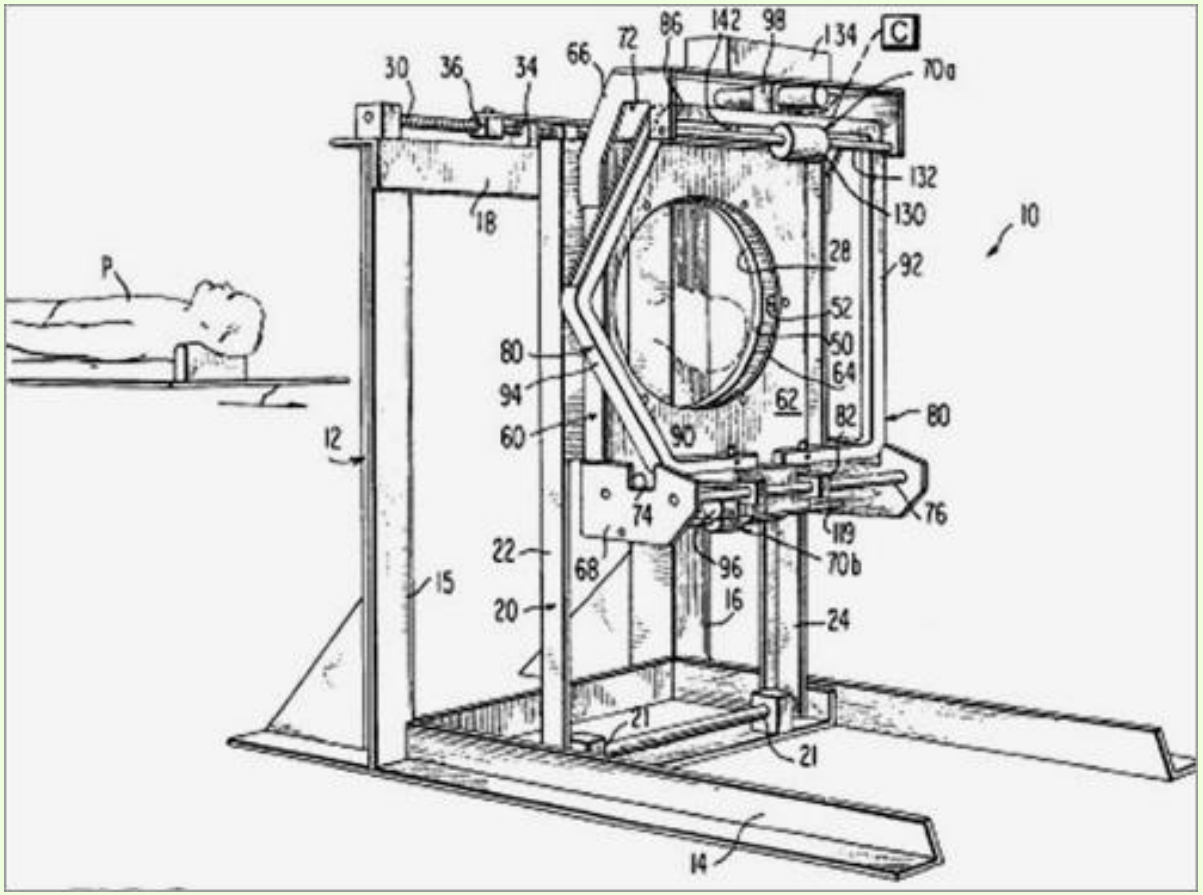
History:
A 45-year-old woman with a history of chronic obstructive pulmonary disease (COPD) presented with cachexia (wasting / “consumption”).

PA and lateral radiographs



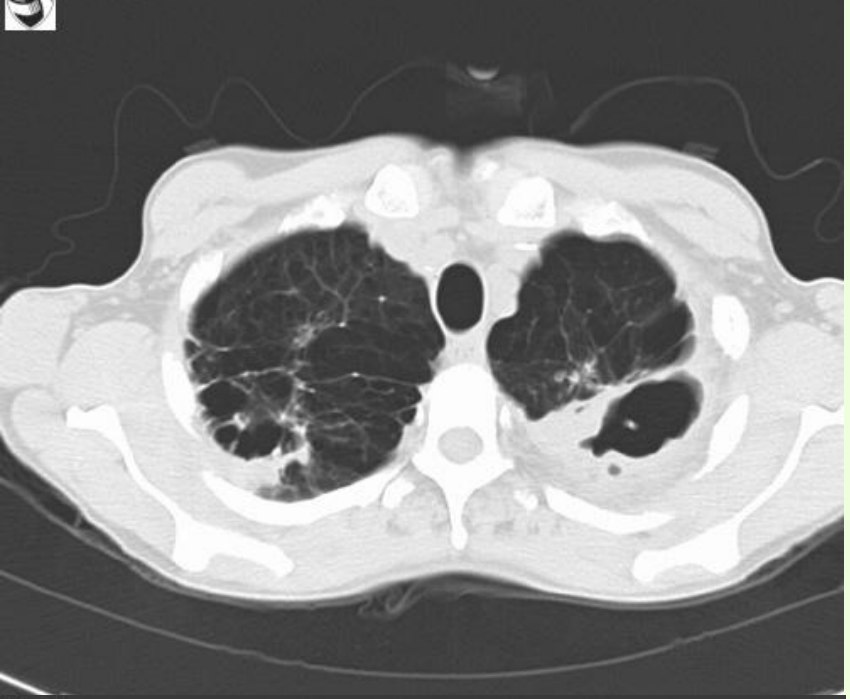
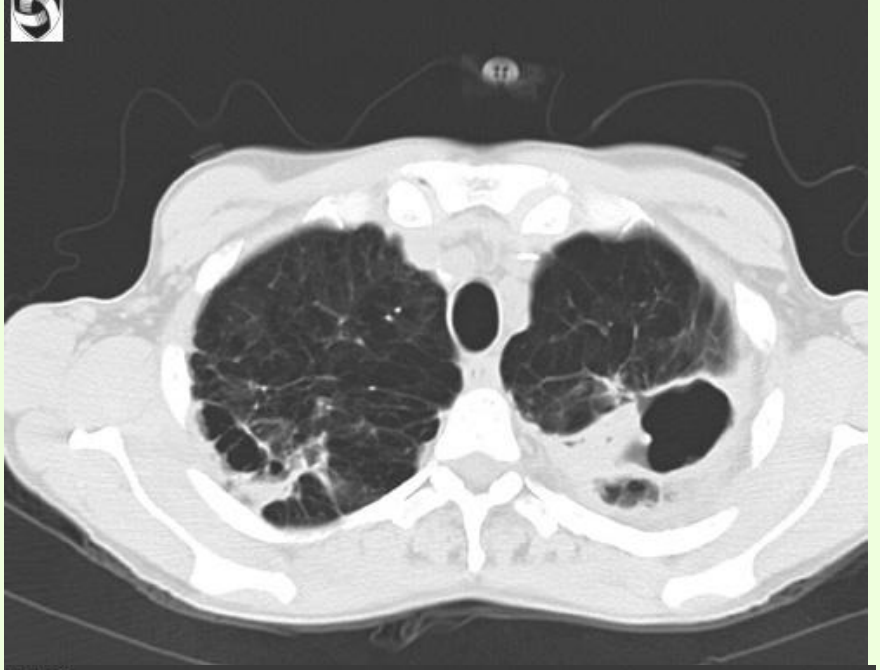
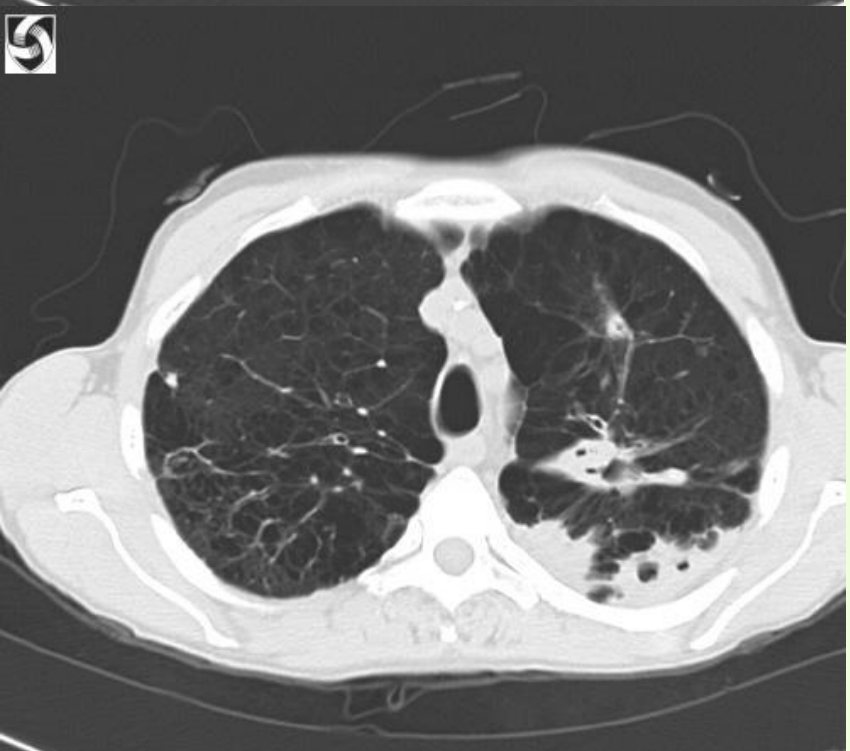
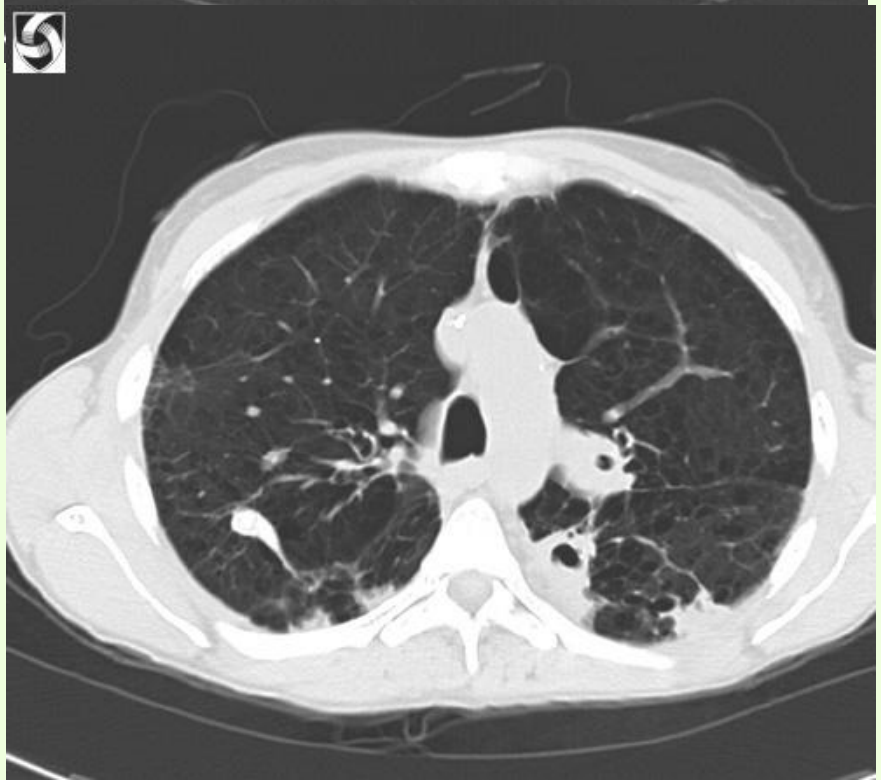


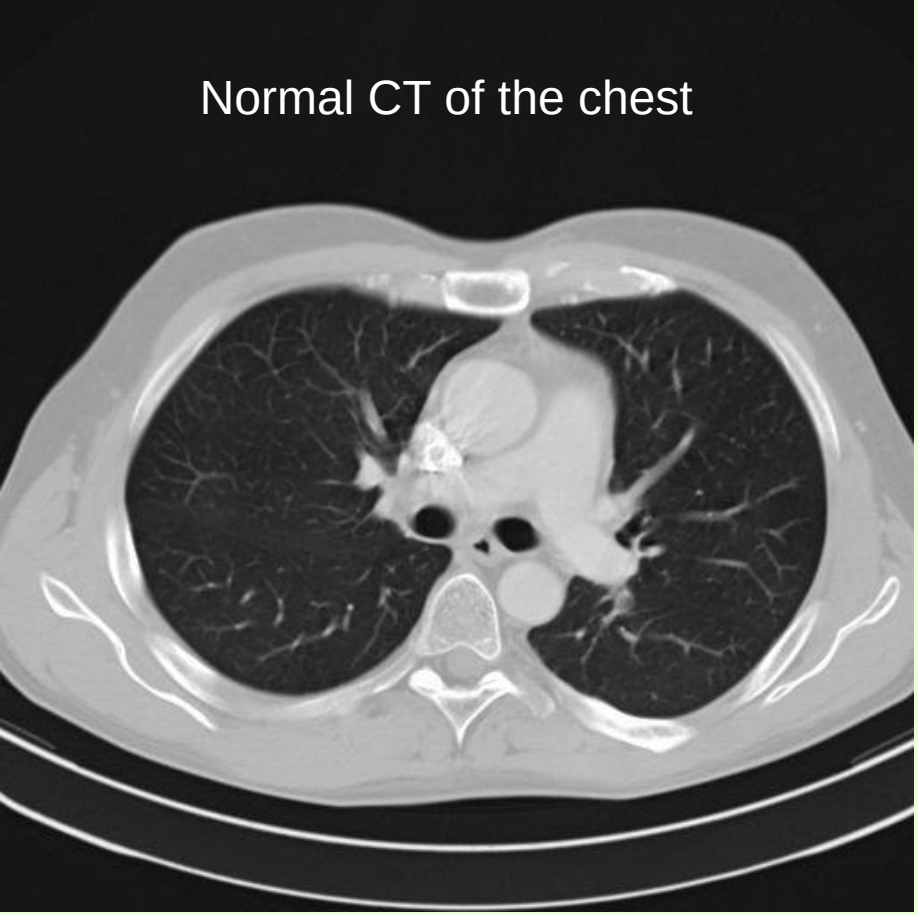
Brief historic review: CT scan

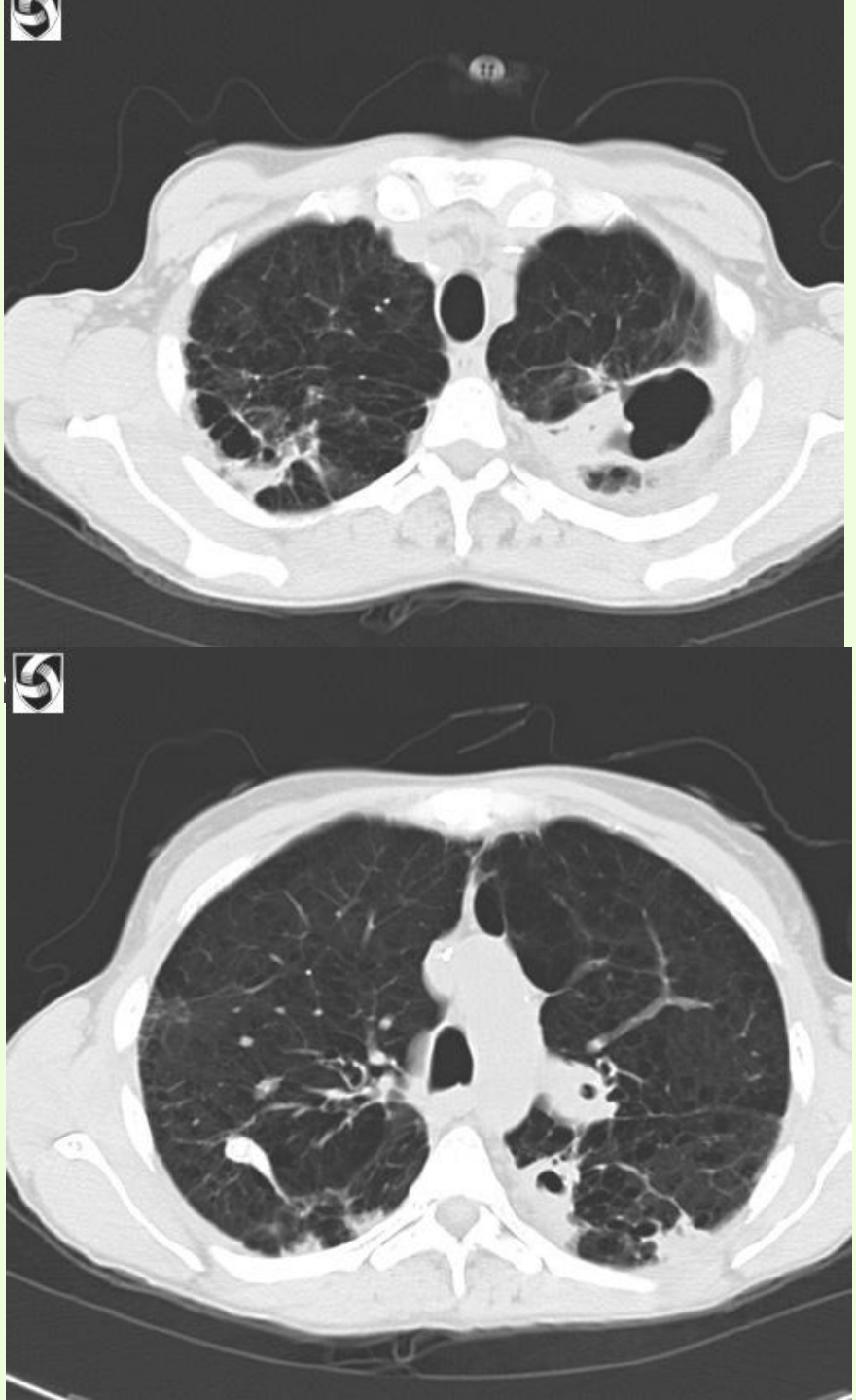


1973, C(A)T scan goes into use in the U.S.

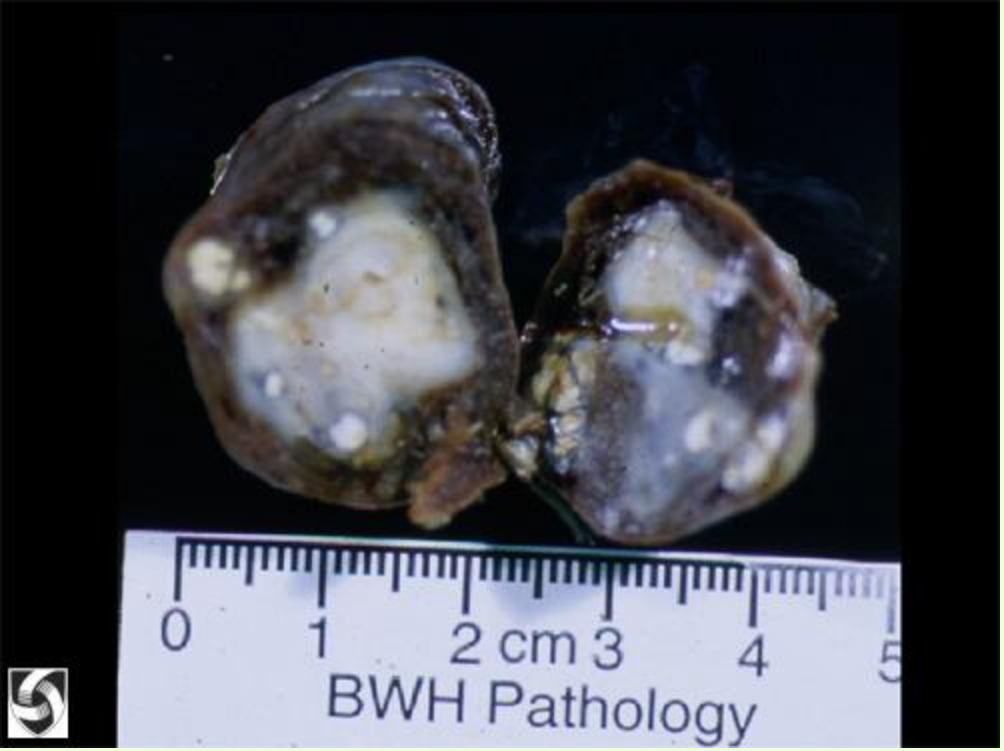
Cormack (Tufts University, Massachusetts, U.S.) and Hounsfield (EMI Central Research Laboratories in England) shared the 1979 Nobel Prize in Physiology or Medicine.

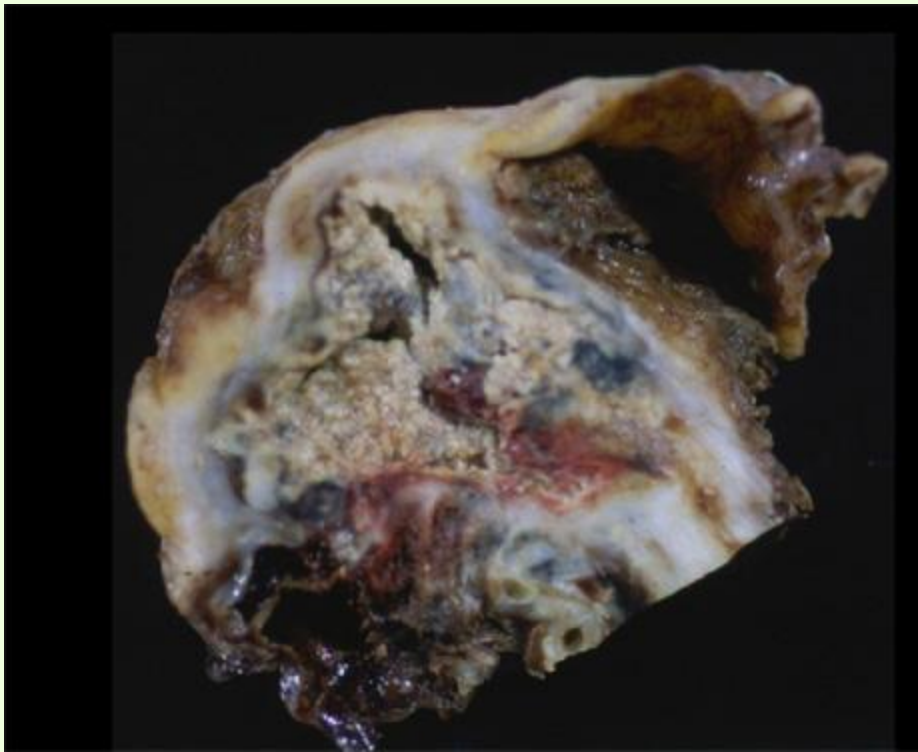


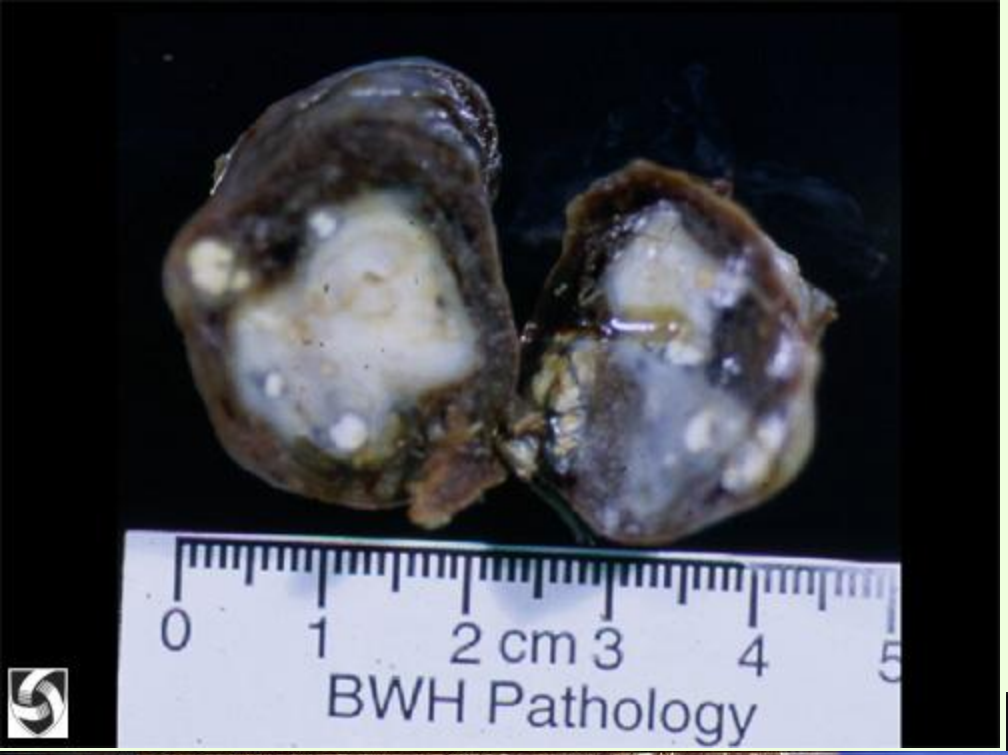


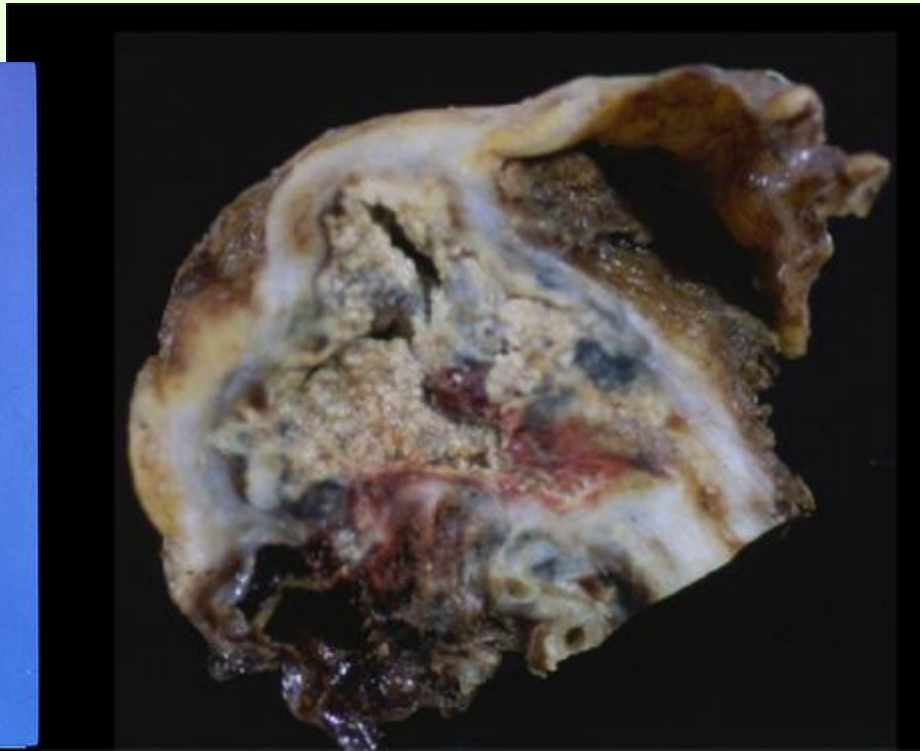
- cavity and some fluid-density bullae in the left upper lobe
- Nodules with central calcification
- areas of consolidative/nodular opacity

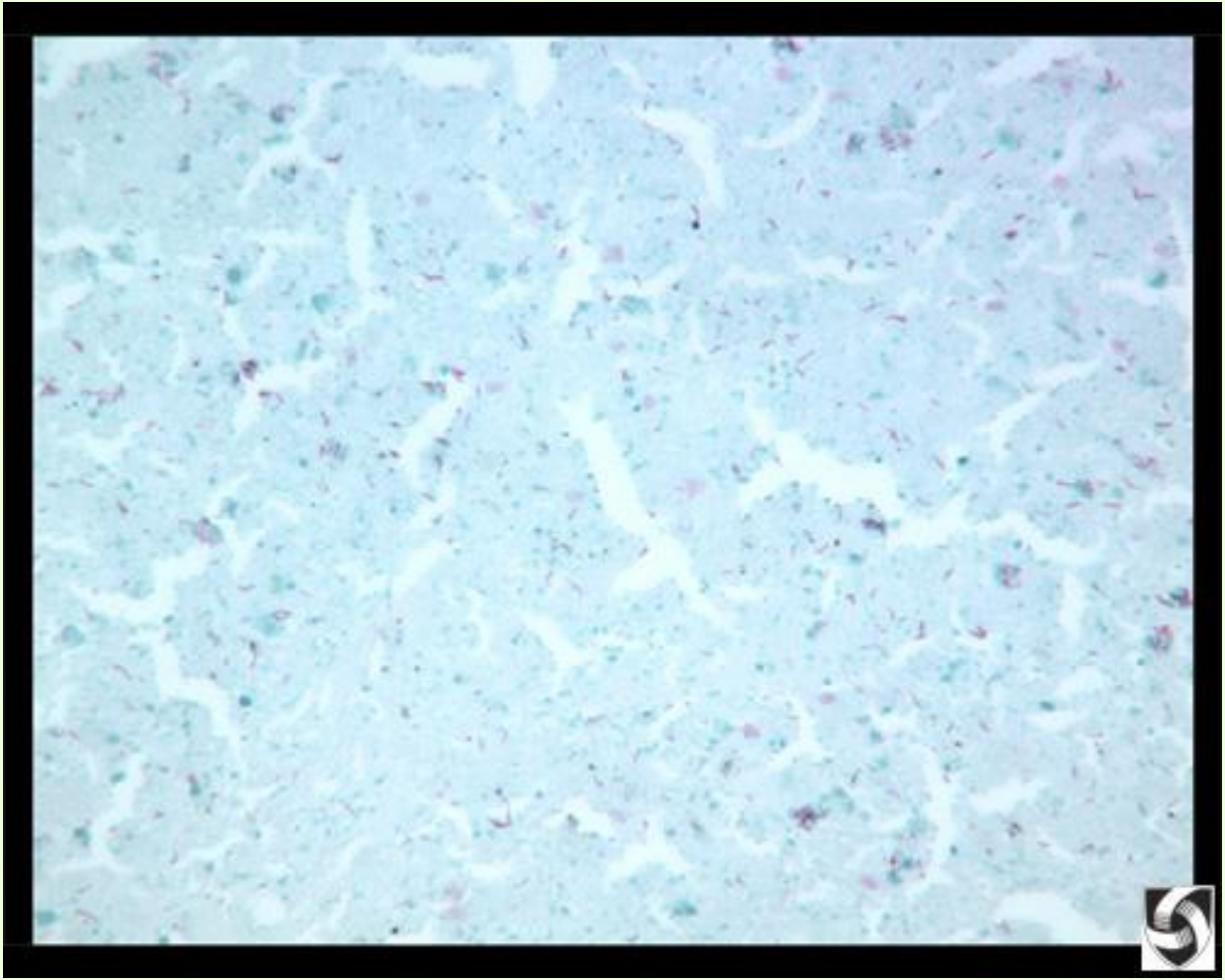


Pat. underwent wedge resection in the areas affected by cavitary lesions:
Tissue appears with cheesy texture throughout.




0 1 2 cm 3 4 5
BWH Pathology



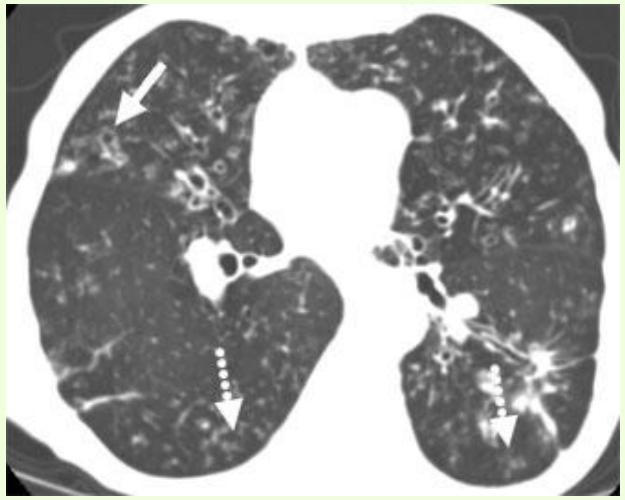


Recommendation for minimum evaluation of a patient suspected of NTM lung disease

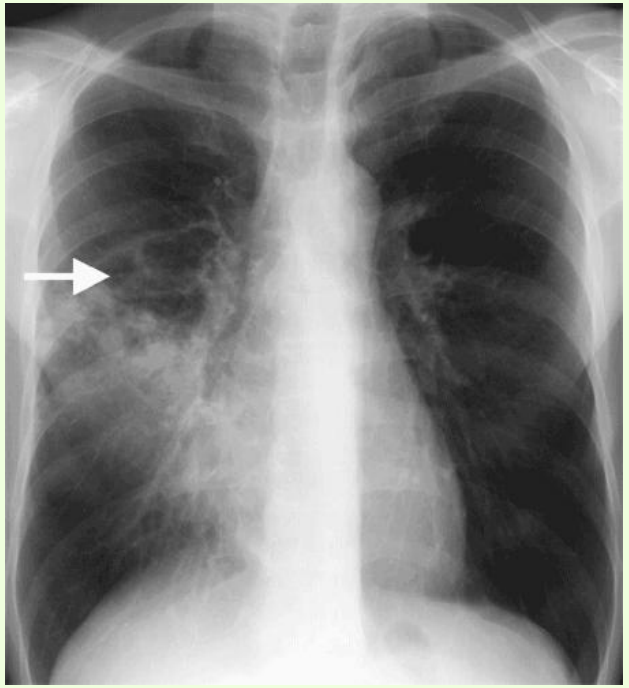
- **Imaging**

  CXR

  → in the absence of cavitation: HRCT



Nodular/ bronchiectatic form



Fibro-cavitary form

- 3 or more s**putum specimens for AFB** analysis

!! Exclude pulmonary TB or other pathologies!!

Diagnostic criteria

- **How to establish and evaluate clinical guidelines**
  - **Leading questions:**

Who gets the disease?

How do we best diagnose the infection (discriminate from disease)?

What‘s the best treatment for each specific disease?

- for the specific clinical site affected
- for the specific pathogen identified

What‘s the optimal length of treatment (adverse effects!)

⇒ Clinical studies
⇒ Daily clinical practice (expert opinion)

} Clinical guidelines

Diagnostic criteria

TABLE 1. THE STRENGTH OF RECOMMENDATIONS BASED ON QUALITY OF EVIDENCE (ADAPTED FROM THE INFECTIOUS DISEASE SOCIETY OF AMERICA/UNITED STATES PUBLIC HEALTH SERVICE RATING SYSTEM)

Categories Reflecting the Strength of Each Recommendation for or against Its Use		Grades Reflecting the Quality of Evidence on Which Recommendations Are Based	
Category	Definition	Grade	Definition
A	Good evidence to support a recommendation for use	I	Evidence from at least one properly randomized, controlled trial
B	Moderate evidence to support a recommendation for use	II	Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), from multiple time-series studies or from dramatic results in uncontrolled experiments
C	Poor evidence to support a recommendation for or against use	III	Evidence from opinion of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees
D	Moderate evidence to support a recommendation against use		
E	Good evidence to support a recommendation against use		

Diagnostic criteria

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)

* For evidence quality, *see* Table 1.

Diagnostic criteria

- **Clinical criteria**

  Pulmonary symptoms

  PLUS

  nodular or cavitary opacities on CXR

  or

  HRCT showing multifocal bronchiectasis with multiple small nodules (A,I)

  PLUS

  Appropriate exclusion of other diagnoses (A,I)

- **Microbiological criteria**

  positive culture results from at least 2 separate Sputum samples (A,II)

  (exception: nodular/bronchiectatic form: 1 positive culture result is enough)

  OR

  positive culture results from at least 1 BAL (C,III)

  OR

  Lung biopsy with mycobacterial histopathologic features and positive culture ***or***

  Lung biopsy with mycobacterial histopathologic features positive culture from sputum/BAL sample

Diagnostic criteria

- Both clinical **AND** microbiological criteria must be fulfilled.
- Expert consultation should be obtained when NTM are recovered that are either infrequently encountered or that usually represent environmental contamination.
- 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.
- Empiric therapy for TB, especially with positive AFB smears may be necessary pending confirmation of the diagnosis of NTM lung disease.
- Making the diagnosis of NTM lung disease does not, *per se*, neccessitate the institution of therapy,

  -> decision based on potential risks and benefits of therapy for individual patients

Diagnostic criteria

- **When to suspect contamination?**

  Only one single sample culture positive

  Isolation of a generally apathogenic species, i.e.

  M. gordonae, M. terrae complex, M. mucogenicum, M. scrofulaceum

  M. simiae, M. lentiflavum

- **Colonisation?** (= colonizing strains without disease)

  Controversal discussion.

  Most experts tend to classify as asymptomatic infection.

- **Patients with cystic fibrosis?**

  Annual screening recommended.

2 Disseminated NTM disease

- **Epidemiology**

  MAC (>90% *M. avium*) >> *M. kansasii* > others

  among the most common and severe infections in **advanced HIV-Infection.**

  - extremely rare before 1980 -> estimated 37.000 cases in 1994

  decreased markedly since then.

  - children with AIDS have rates of disseminated MAC disease similar to adults

  very rare: RGM → post-TPL, long-term steroids, leukaemia

- **Clinical presentation**

  unspecific: malaise / systemic symptoms, abdominal pain, diarrhoea

2 Disseminated NTM disease

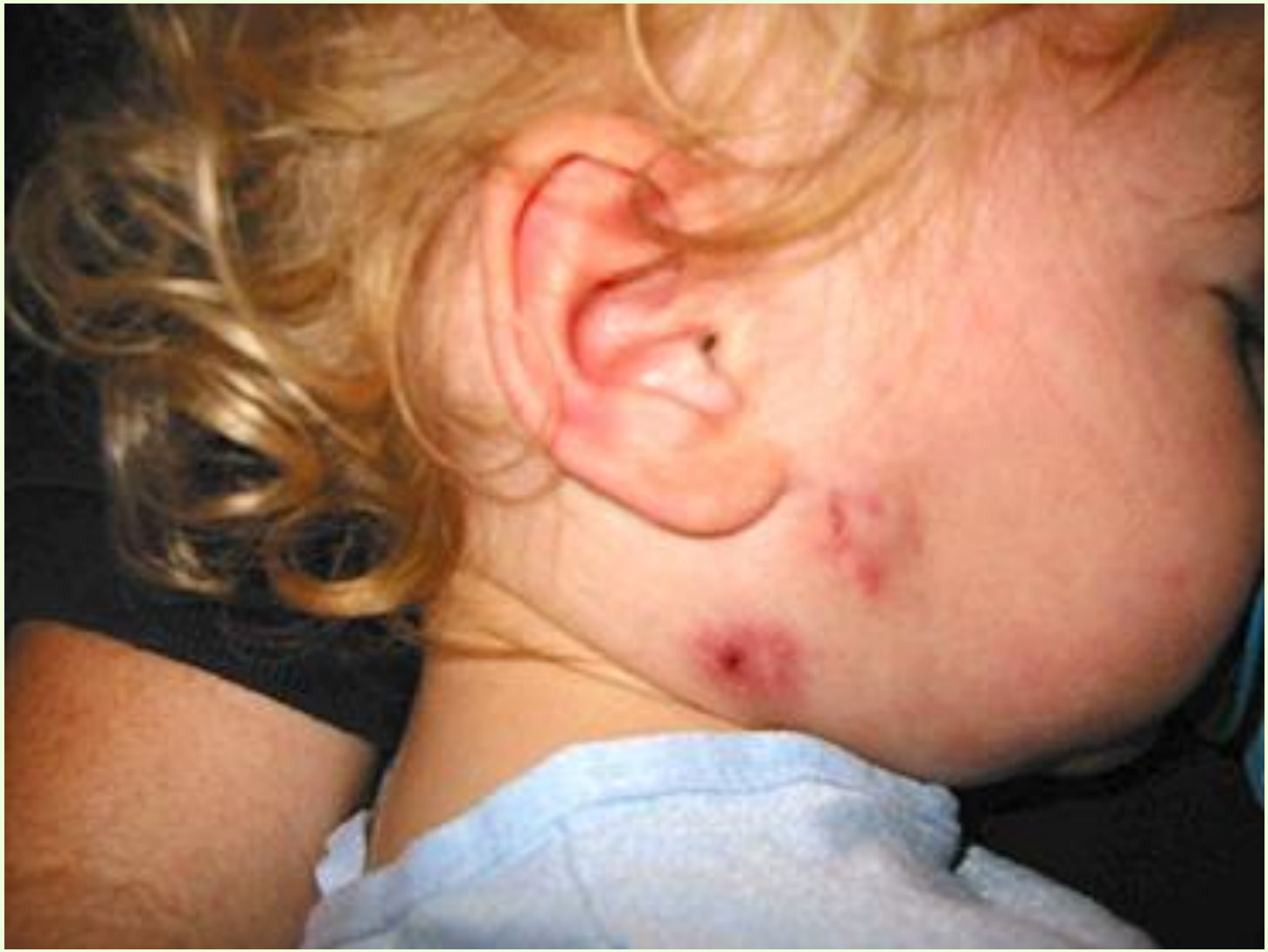
- **Diagnostics**
  - Blood tests: anaemia, AlkPhos↑, LDH↑ (chronic inflammatory process)

  - diagnosis made form 2 positive blood cultures;
  - In case of 2 negative B/C in a symptomatic patient

  → send BM aspirate or liver biopsy for culture

  - NOTE: NTM isolate in a pulmonary sample of an HIV/AIDS-patient is rarely associated with pulmonary disease but often with subsequent dissemination!

Cervical Lymphadenitis



3 Lymphatic disease

- **Epidemiology**

  Cervical adenitis: most common form of NTM disease in **children (1-5 yrs)**

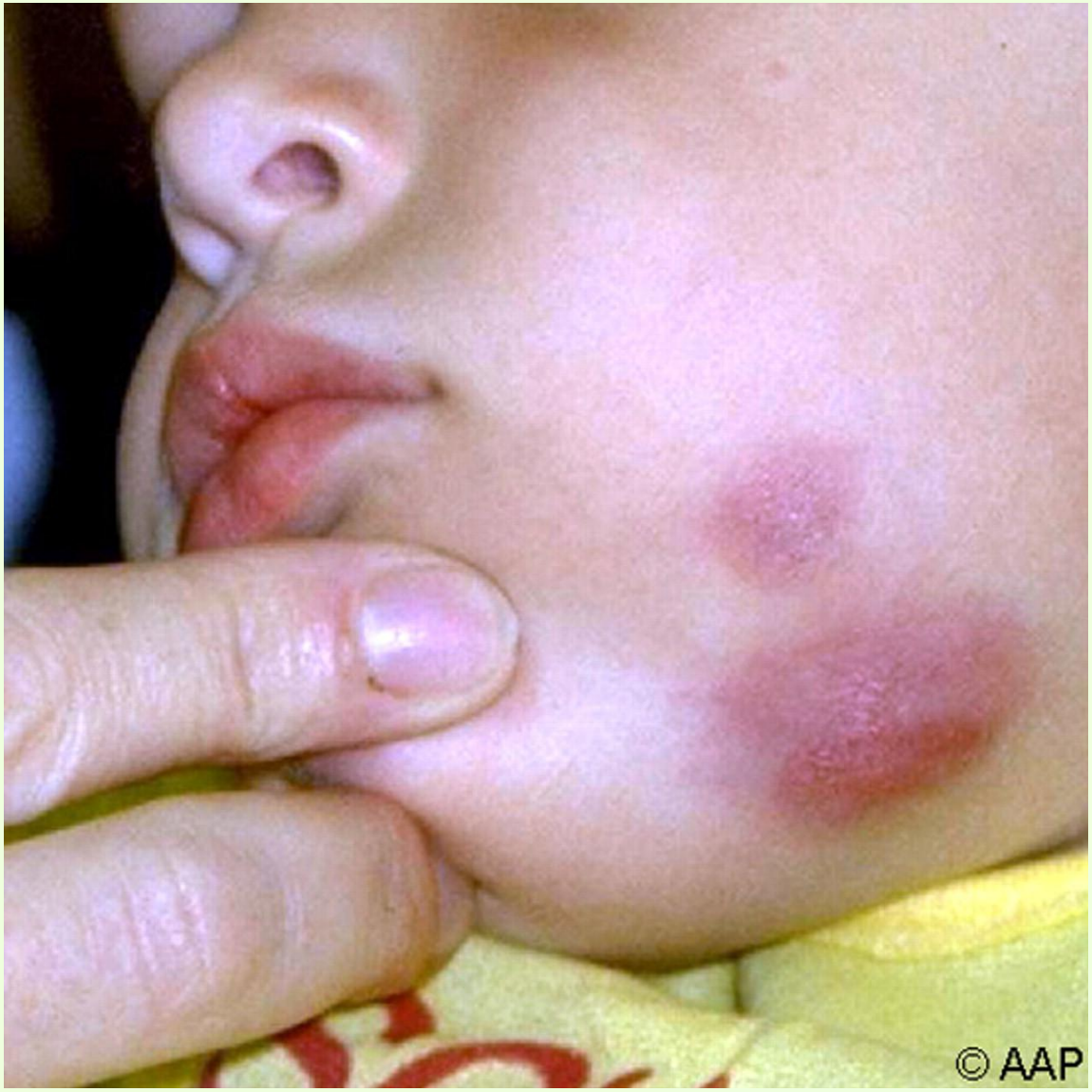
  MAC (80%) >> *M. scrofulaceum* (USA) / *M. malmoense, M. Haemophilum* (Europe)

- **Clinical presentation**

  Occurs insidiously, rarely associated with systemic symptoms.

  95 % unilateral, **non-tender,** enlarge rapidly, may even rupture.

Cervical Lymphadenitis



Cervical Lymphadenitis

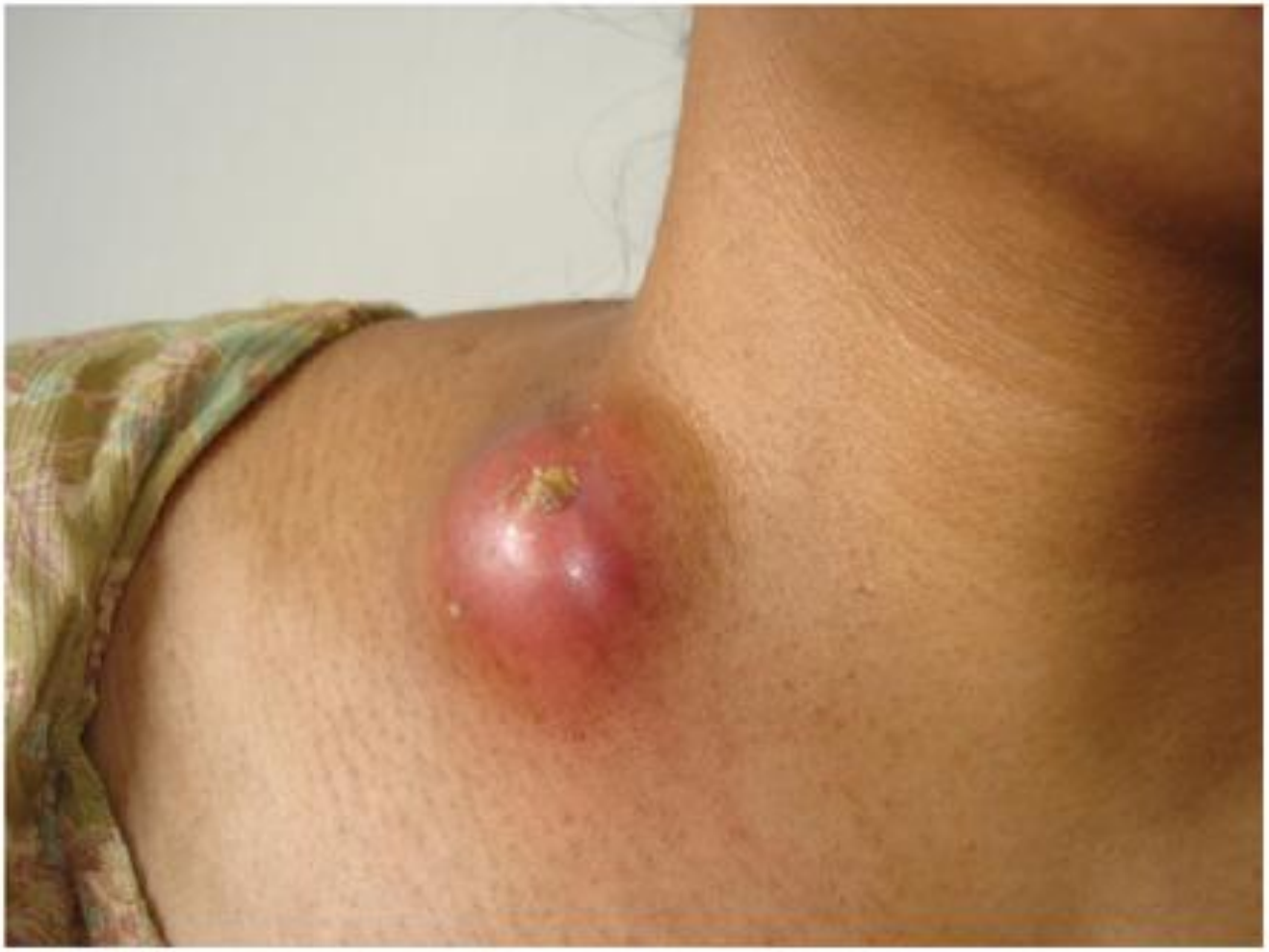


Fig. 1 : Young girl with inflamed, swollen, soft and fluctuant cervical lymph node leading to abscess formation

3 Lymphatic disease

- **Diagnostics**

  Main DD: Tuberculosis

  In children: **MTB** accounts for about **10%** of culture-proven mycobacterial cervical LA (**in the U.S.)** vs. for about 90% in adults!

  Histological findings (caseating granulomata) + TST neg

  OR

  Excisional biopsy (positive culture in about 50 – 82 %)

- **Therapy (in the immunocompetent)**

  Complete surgical excision without treatment

4 Skin, Soft tissue and skeletal NTM disease

- **Epidemiology**

  Virtually **all** species have been described as cause of cutaneous disease

  Mainly RGM (*M. fortuitum, abscessus, chelonae*), *M. marinum, M. ulcerans*

- **Clinical presentation**

  Localized drainage or abscess formation at the site of puncture wounds or

  open traumatic injuries, nosocomial (RGM) infections:

  i.e. long-IV lines or peritoneal catheters, post-injection abscesses, infections after liposuction, or surgical wound infections.

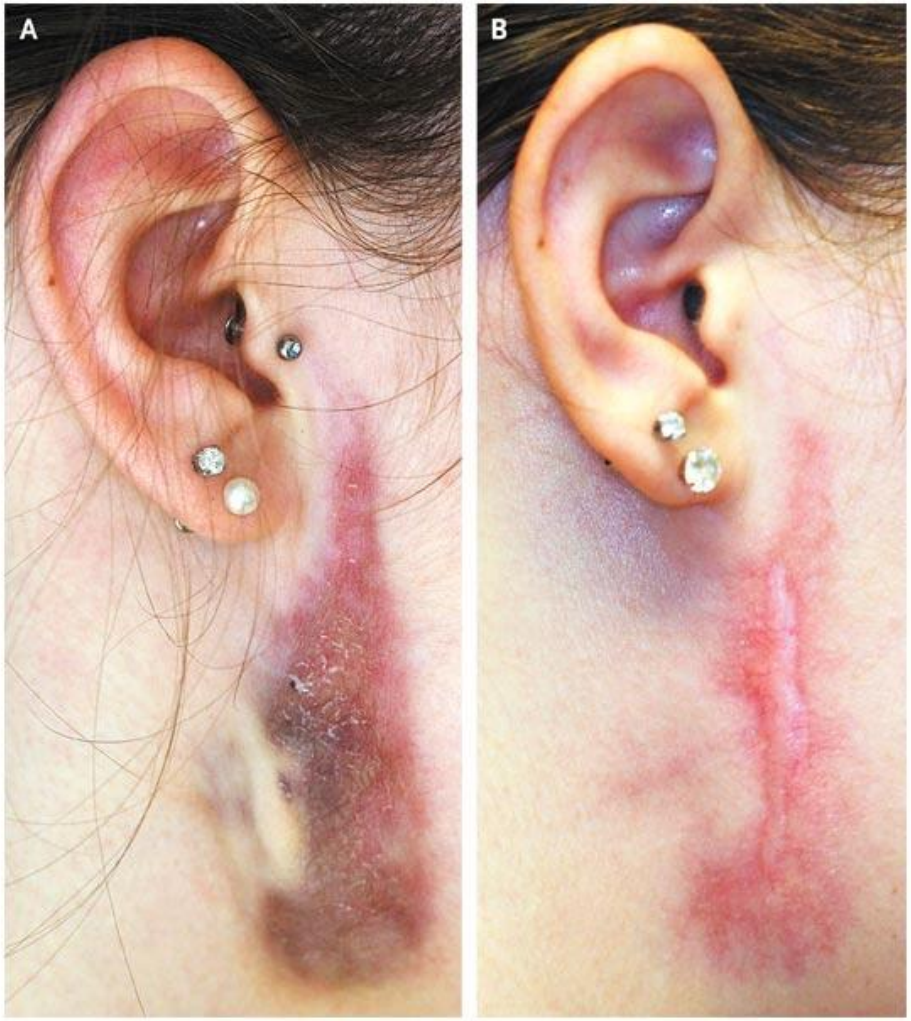
- **Diagnosis**

  made through biopsy

- **Therapy**

  surgical débridement AND antimycobacterial therapy

4 Skin, Soft tissue and skeletal NTM disease



Clinical case

18yr old: Large, fluctuant, violaceous plaque on her right cheek 6 months after professional piercing of the tragus.
Abscess drainage & Cephalexin Tx.
No improvement.
Biopsy performed: AFB pos. And culture grew: *M.fortuitum*.
4-mo multidrug Tx.

Piercing-Related **NTM** Infection.
Kimberly A. Horii, M.D., and Mary Anne Jackson, M.D.
N Engl J Med 2010; 362:2012May 27, 2010

Therapy

- **General thoughts / comments**

Every clinical NTM isolate must always evaluated in the clinical context

- Contamination? Asymptomatic infection or clinical disease?

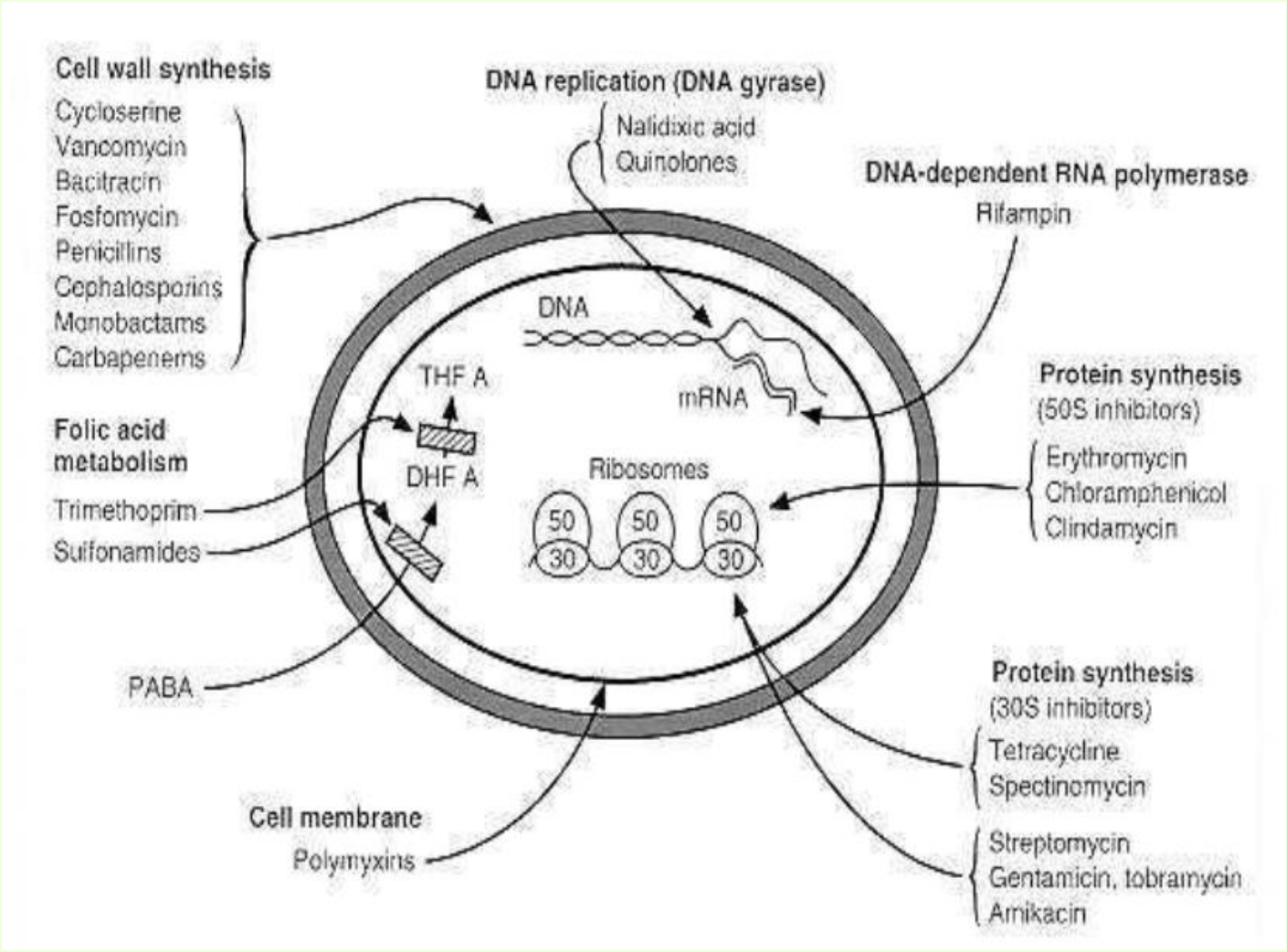
Therapeutic recommendations for infrequently encountered NTM species are based on only a few reported cases. Thus, treatment duration is based on treatment recommendations for more frequently encountered NTM species, such as MAC.

in vitro resistance testing does **not neccessarily** correlate with clinical response

Empiric treatment for suspected NTM lung diseaes is NOT recommended

There are no criteria for surgical treatment in pulmonary NTM disease

Mechanisms of action



Mycobacterium avium Complex (MAC)

- **Pulmonary disease**

	Initial Therapy for Nodular/Bronchiectatic Disease*	Evidence Quality†	Initial Therapy for Cavitary Disease	Evidence Quality†	Advanced (Severe) or Previously Treated Disease
Macrolide	Clarithromycin 1,000 mg TIW or azithromycin 500–600 mg TIW	B, II	Clarithromycin 500‡–1,000 mg/d or azithromycin 250–300 mg/d	A, II	Clarithromycin 500‡–1,000 mg/d or azithromycin 250–300 mg/d
Ethambutol	25 mg/kg TIW		15 mg/kg/d		15 mg/kg/d
Rifamycin	Rifampin 600 mg TIW		Rifampin 450‡–600 mg/d		Rifabutin 150‡–300 mg/d or rifampin 450‡–600 mg/d
IV aminoglycoside	None		Streptomycin or amikacin§ or none		Streptomycin or amikacin§

Definition of abbreviations: IV = intravenous; TIW = three times weekly.
* Not recommended for severe or previously treated disease.
† Rating for entire multidrug regimen, not necessarily for individual agents. For evidence quality, *see* Table 1.
‡ Lower dose for weight < 50 kg.
§ *See* text for dosing recommendation.

12 months of negative sputum cultures while on therapy!

Macrolide-resistent isolates

therapeutic approach difficult and discussed controversially

maybe surgery PLUS IV aminoglycoside

Mycobacterium avium Complex (MAC)

- **Pulmonary disease – treat or wait & see?**

Patients with **nodular/bronchiectatic** disease:

- treat or
- Wait & see, **IF**…
  - … only minimal clinical symptoms and radiologial changes
  - … (life-long) follow-up provided (clinical, microbiological and imaging (HRCT).

Patients with **fibro-cavitary** disease in the upper lobes:

- Treat ALL!

Mycobacterium avium Complex (MAC)

complex lung disease – surgical options

***Context*:**

1. There are no established criteria for patient selection.
2. There are potentially severe perioperative complications.
3. There are few centers with extensive experience with mycobacterial surgery.

***Recommendations*:**

1. Surgical resection of limited (focal) disease in a patient with adequate cardiopulmonary reserve to withstand partial or complete lung resection can be successful in combination with multidrug treatment regimens for treating MAC lung disease (B, II).
2. Surgical resection of a solitary pulmonary nodule due to MAC is considered curative (C, III).
3. Mycobacterial lung disease surgery should be performed in centers with expertise in both medical and surgical management of mycobacterial diseases (C, III).

Mycobacterium avium Complex (MAC)

disseminated disease in HIV patients

- Treatment should be considered as life-long, unless immune restoration is achieved by HAART (min CD4 count >100 cells/ul for >12 mo)
- No routine monitoring unless symptoms of active MAC infection

Preferred (A, I)*	Alternative (B, I)*
Treatment	
Clarithromycin 500 mg orally twice daily + Ethambutol 15 mg/kg orally daily ± Rifabutin† 300 mg orally daily	Azithromycin 500 mg daily + Ethambutol 15 mg/kg daily ± Rifabutin† 300–450 mg orally daily
Prevention‡	
Azithromycin 1,200 mg orally weekly	Clarithromycin 500 mg orally twice daily or Rifabutin† 300 mg orally daily

Mycobacterium avium Complex (MAC)

- **Skin, soft tissue, skeletal disease**

  Excisional surgery or surgical débridement

  AND

  multi-drug anitmycobacterial therapy for 6-12 months

- **Lymphadenitis**

  Excisional surgery without antimycobacterial therapy is the treatment of choice

  NOTE

  Child with granulomatous disease +/- AFB on LN excised LN **AND**

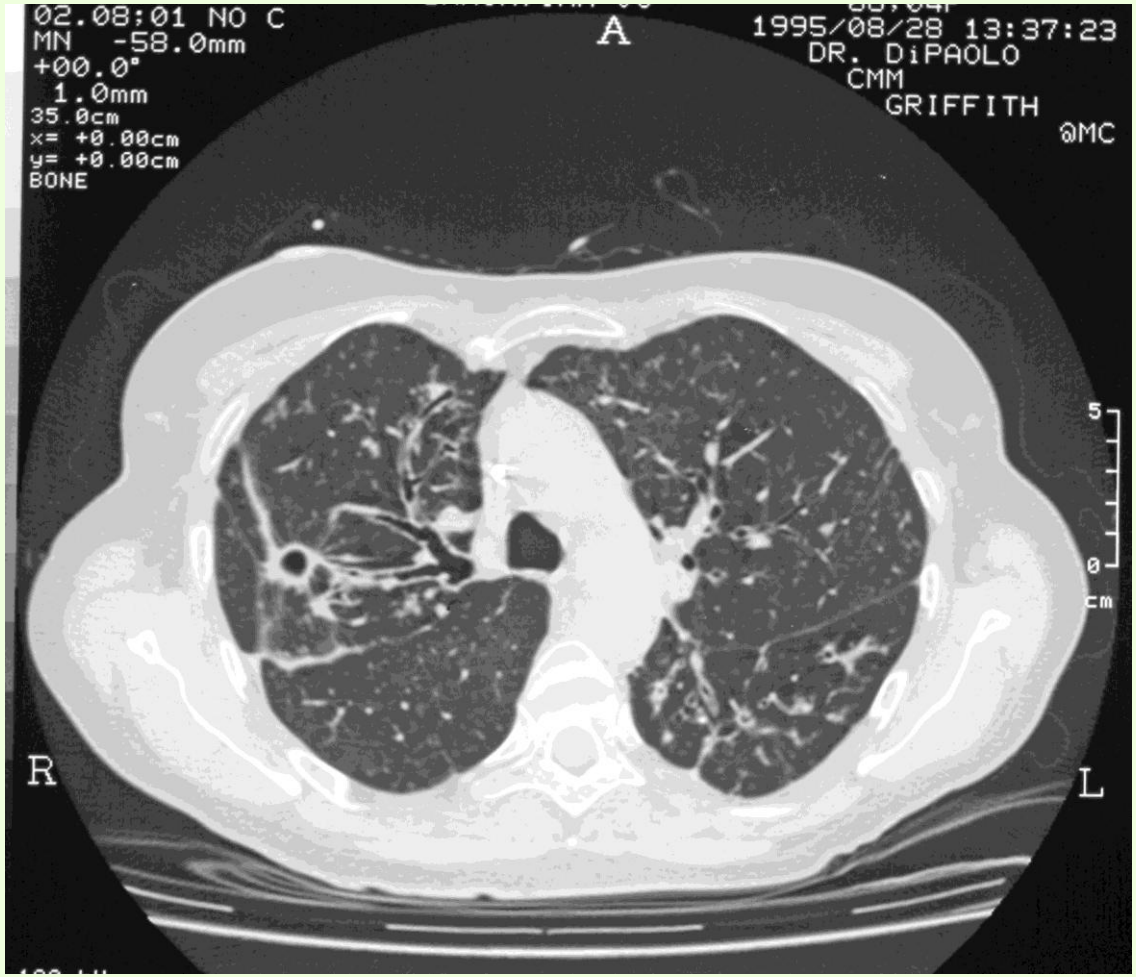
  TST positive

  → start anti-TB therapy pending culture results

  a) if neg: stopp treatment

  b) if pos for NTM: switch to appropriate regimen

Mycobacterium abscessus (RGM)



Clinical case

Chest CT:
70 year-old female, non-smoker, with *M. abscessus* disease showing nodules, bronchiectasis and cavitation.

Preventative measures

What would you recommend?

- Don‘t expose wounds, IV catheters or any other clinical devices used for invasive procedures to tap water
- Avoid contamination of clinical devices / equipment with water or ice
- Ask patients not to drink water bevor taking sputum samples
- In individuals at risk: maybe beneficial to avoid showers and aerosols from tap water?
- Hand hygiene!!

What research still needs to be done

- **Epidemiology:**
  incidence / prevalence rates including geographic differences
  potential risk factors
  Problem: NTM disease occures sporadically, not reported to PH authorities

- Identifying the **source(s) of infection**. The specific reservoire.
  -> help with disease prevention

- What‘s the **role of immune factors** in disease development for patients with NTM disease?
  (IFNγ and IL-12 synthesis and response pathways are known to play a role)

- In contrast to TB, in NTM disease reliable information on **drug therapy** (PK and PD) as well as therapy monitoring remain to be elucidated. Efficacy studies for many individual agents in the treatment of NTM disease is not available
- Maybe elevating NTM in the rank of „emerging pathogens“ would increase funding opportunities...

Questions to consider

- What are non-tuberculous mycobacteria (as opposed to MTB)?
- What are the clinical manifestations of NTM infection -> disease
- How do I define the difference between NTM infection and disease?
- Actually, who suffers from NTM disease?
- What are the current diagnostic recommendations?
- How well established are our therapeutic regimens?
- What do we still need to do?

Take home message

- Clinical Infectious diseases: a complicated host-pathogen interplay that involves a thorough work-up of every individual‘s scene

- mycobacterium ≠ mycobacterium

- Therapeutic approach varies according to species identified

- Positive microbiological results does not neccessarily mean infection. **Always exclude TB!**

- Still a vast open plane of unknown territory
- Controversial views, guidelines not always straight-forward

  → based on case reports and / or expert opinon