TB AND NON-TB MYCOBACTERIAL INFECTION UPDATE 2020

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DISCLOSURES AND OBJECTIVES

Disclosures

No disclosures

Outline/ Objectives

- TB Stats from Erie County
- (Brief) History of TB
- Diagnosing Active TB
- Treatment of Active TB
- Latent TB
  - Diagnosis
  - Treatment
- Non-Tuberculous Mycobacteria

MISCONCEPTIONS TO DISPEL

FALSE IDEAS aka "Fake News"	TRUE FACTS
• • TB in Erie County is mostly seen in prison inmates, homeless people, and patients with HIV/ AIDS. • • TB cases are almost always positive on sputum smear • • Extrapulmonary TB is very rare • • Miliary TB is a synonym for severe or "bad" TB, such as extensive cavitary disease. • Lung cavities are almost always due to TB.	• TB in Erie County, like elsewhere in the U.S., is increasingly seen in the foreign-born population • The majority of TB cases in Erie County are diagnosed by + sputum culture but (-) on smear. • About 30 % of TB cases are extra-pulmonary. • Miliary TB is a distinct syndrome, almost always smear negative and non-cavitary. • Cavitary lung lesions have a broad DDx.

MISCONCEPTIONS TO DISPEL

FALSE IDEAS aka “Fake News”	TRUE FACTS
• • Patients need to be sent to the hospital for admission in order to collect sputum specimens for AFB • • Non-compliance with TB treatment regimens is the reason fora high incidence of treatment failures or relapses in Erie Co.	• Sputum specimens for AFB can be collected at home and brought to the laboratory by a family member. First am sputums are the best. • TB treatment in Erie County and in most places is by directly observed therapy (DOT). • Successful treatment with durable cure is obtained in > 95 % of TB cases. • Subsequent TB in a patient previously treated for TB is often by exogenous re-infection with a different TB strain.

TB STATISTICS

- TB in Erie County

Tuberculosis Cases in Erie County
2006-2016

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
TOTAL	11	9	16	15	11	14	19	21	16	13	13
Born Outside the U.S.	8	5	8	6	5	8	13	16	11	11	7
% Born Outside U.S.	72.7	56.0	50.0	40.0	45.5	57.1	68.4	76.2	68.8	84.6	53.8
Known AIDS	0	1	1	0	0	1	0	2	0	0	0
Homeless	0	0	0	0	0	0	0	0	0	0	0
Inmates	0	0	0	0	0	0	0	0	0	0	0
Nursing Home	0	0	0	0	0	2	0	1	0	0	0
Pulmonary	7	5	14	11	7	12	14	16	12	10	9
X-Pulmonary	2	5	3	4	4	3	7	6	5	8	4
Culture (+)	9	8	13	12	8	11	16	17	11	9	12
Smear (+)	6	2	7	4	4	6	4	6	5	6	2

DESCRIPTIVE STATISTICS

Tuberculosis Cases by Race, Ethnicity, and Age (Percent of Cases) 2006-2016

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
White	27.3	44.4	25.0	46.7	0.0	42.9	36.8	28.6	25.0	7.7	30.7
Black	36.3	11.2	37.5	40.0	36.4	35.7	21.1	28.6	6.2	23.1	23.1
Asian	36.4	44.4	31.25	13.3	63.6	21.4	36.8	38.1	68.8	69.2	38.5
Pacific Is.	0.0	0.0	6.25	0.0	0.0	0.0	5.3	4.7	0.0	0.0	0.0
Am. India	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	7.7
Not State	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total	100	100	100	100	100	100	100	100	100	100	100
White/ Hispanic	0.0	11.1	0.0	13.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Black/ Hispanic	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total/ Hispanic	0.0	11.1	.0.	13.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0
<15	0.0	0.0	12.5	13.3	9.1	0.0	5.3	0.0	0.0	15.4	7.7
15-24	18.2	22.2	12.5	20.0	18.2	28.6	0.0	4.7	25.0	15.4	15.4
25-39	18.2	33.3	25.0	13.3	18.2	14.3	21.1	23.8	43.75	30.7	23.1
40-65	27.2	11.2	31.25	13.3	36.4	35.7	47.3	52.4	18.75	38.5	46.1
65+	36.4	33.3	18.75	33.3	18.2	21.4	26.3	19.1	12.5	0.0	7.7
Total	100	100	100	100	100	100	100	100	100	100	100

IMPACT OF COVID-19 ON TB

GLOBAL HEALTH

'The Biggest Monster' Is Spreading. And It's Not the Coronavirus.

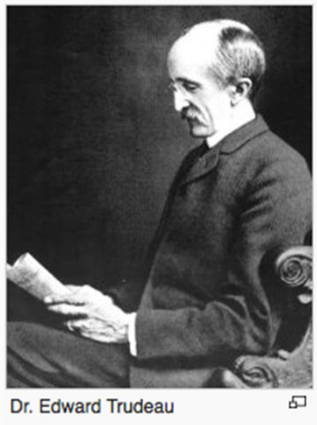
Tuberculosis kills 1.5 million people each year. Lockdowns and supply-chain disruptions threaten progress against the disease as well as H.I.V. and malaria.

" Covid-19 has set back TB control efforts by 20 years…."

HISTORY OF TB

Jean Villemin
transmitted the disease TB from infected sputum to guinea pigs, 1865

M. tuberculosis, 1882



Founder of the Sanatorium Movement in the U.S.

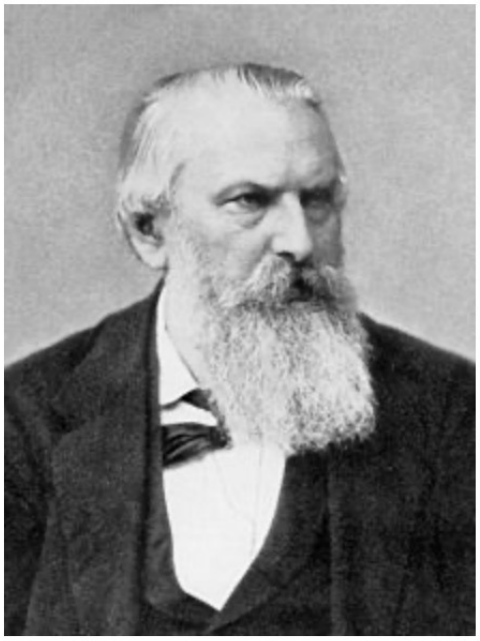
And of the American Lung Association and the American Thoracic Society

Dr. Gardner Middlebrook, developed liquid media for TB and non-TB mycobacteria

HISTORY OF TB, CONT'D

Hermann Brehmer

Hermann Brehmer (14 August 1826 – 28 December 1889) was a German physician who established the first German sanatorium for the systematic open-air treatment of tuberculosis.

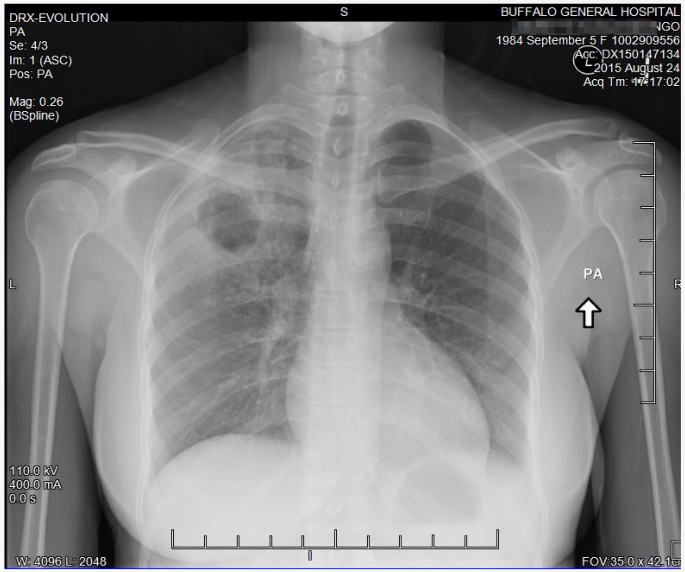


Hermann Brehmer.

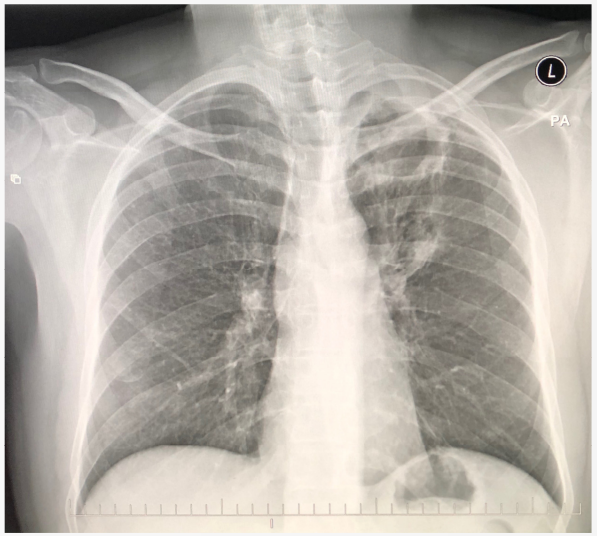
DIAGNOSIS OF ACTIVE TB- EASY WHEN IT IS A CLASSIC CASE

Classic presentation

Nurse from the Democratic Republic of Congo



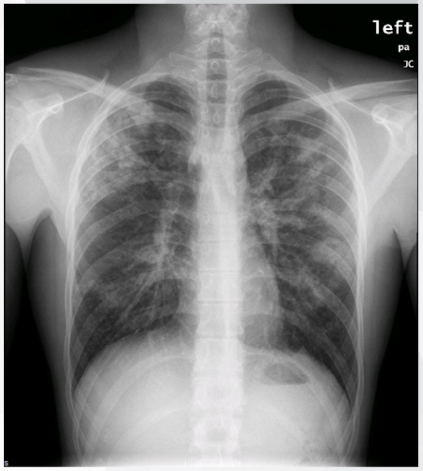
DIAGNOSIS OF ACTIVE TB- EASY WHEN IT IS A CLASSIC CASE



DIAGNOSIS OF ACTIVE TB

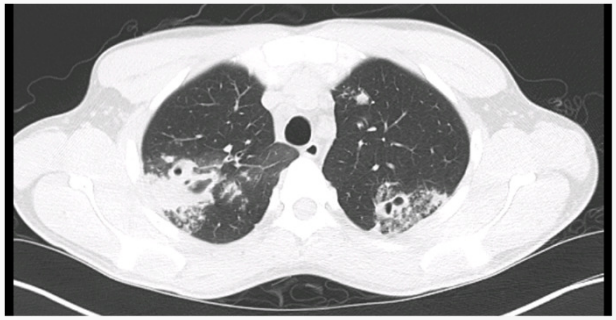
Easy When it is a Classic Case

24 y.o. graduate student from India with 8 lb. weight loss, loss of appetite, tired and weak; mild cough; T to 101 º F



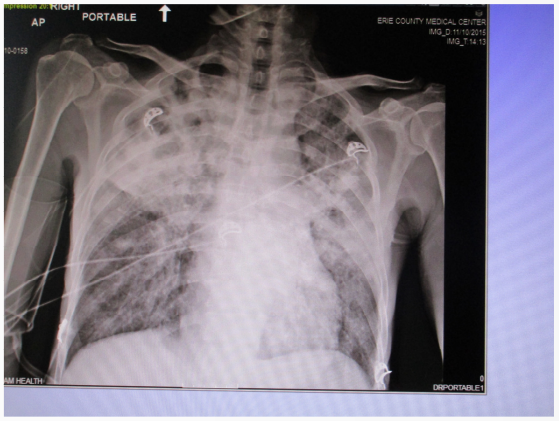
DIAGNOSIS OF ACTIVE TB

Classic presentation-
Upper Lobe
Cavitary Disease



ANOTHER "SORT-OF" CLASSIC CASE

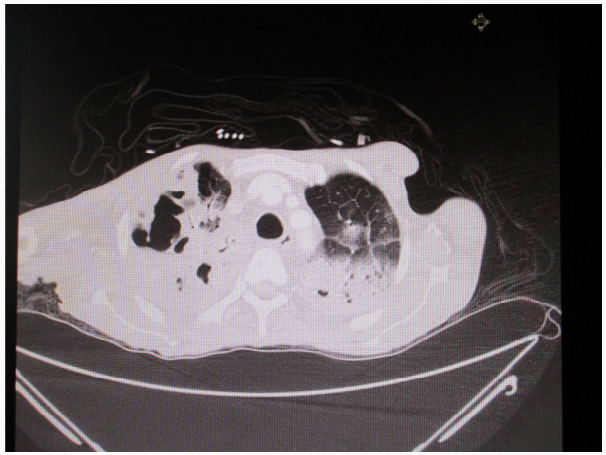
57 y.o. man from Burma who presented to the hospital with shortness of breath and upper lobe disease.



SCOUT FILM OF THE CT SCAN

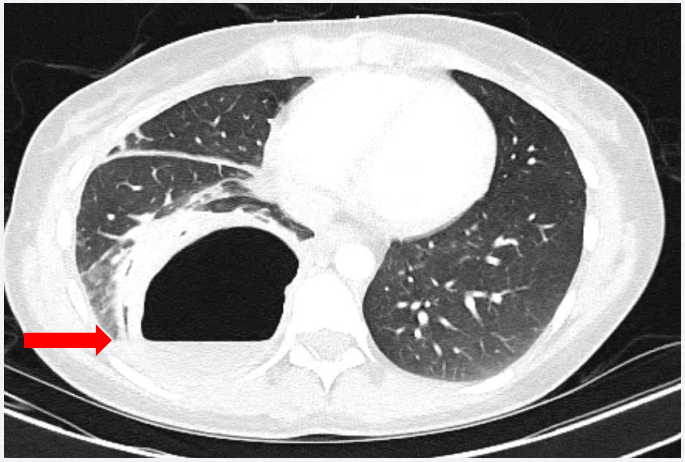
He was intubated and admitted to the MICU.
Multiple sputum were 4 + positive for AFB

CT SCAN



He was started on 4-drug anti-TB therapy
but he required high FIO2's of 60-90 %, was often hypotensive, and he had persistent lactic acidosis.
All other bacterial cultures were negative.
He died on the 13th ICU day of worsening hypoxia and hypotension.
He grew *M. tb* that was pan-sensitive.

Radiographic Clues that It Might NOT be TB



What is the clue indicated by the arrow and what is the diagnosis ?

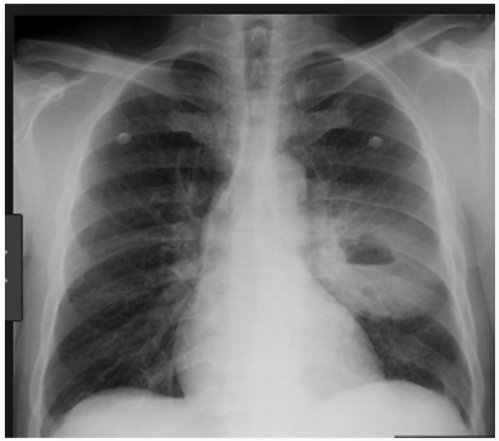
CAVITARY LUNG LESIONS- MORE THAN JUST TB

- Single Large Cavity in the RLL with a distinctive finding.
- h/o seizures
- Foul -Smelling Breath
- Elevated WBC w/ left shift

Pediatric Lung Abscess

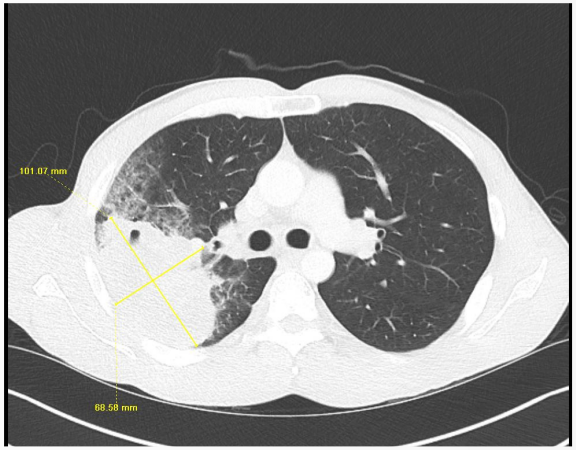
CAVITARY DISEASE

- Anaerobic Lung Abscesses
- Not just in the RLL



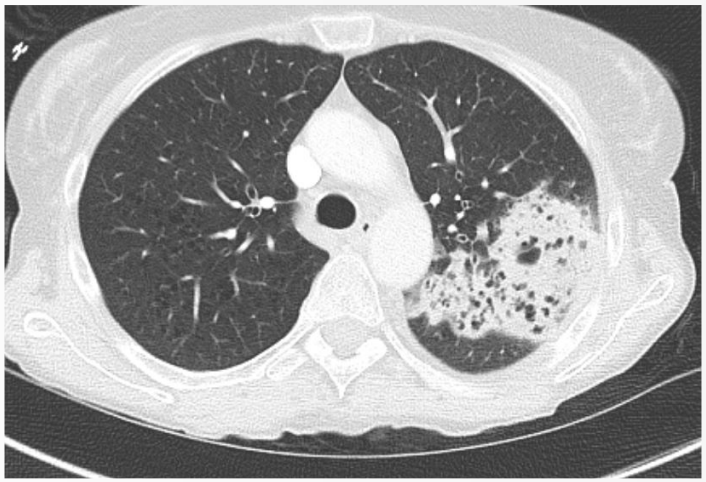
A 46 Y.O. MAN WITH BAD DENTITION AND RECENT DENTAL WORK

Routine sputum cultures showed normal flora only;
AFB specimens were (-) on smear and on culture.



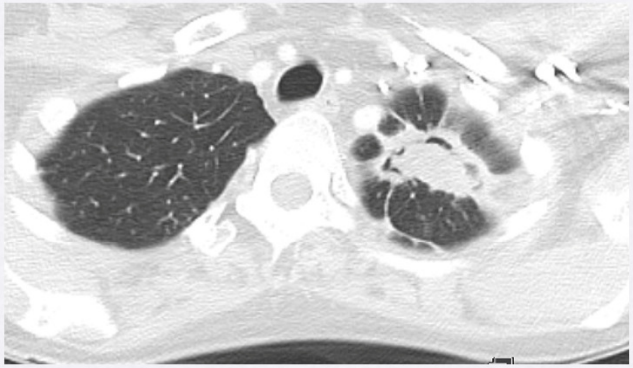
WHAT ARE THE CLUES SHE MIGHT NOT HAVE TB ? (54 Y.O. WOMAN WITH SEVERAL PREVIOUS HOSPITAL STAYS)

Routine cultures grew 3+ *Acinetobacter baumannii.*



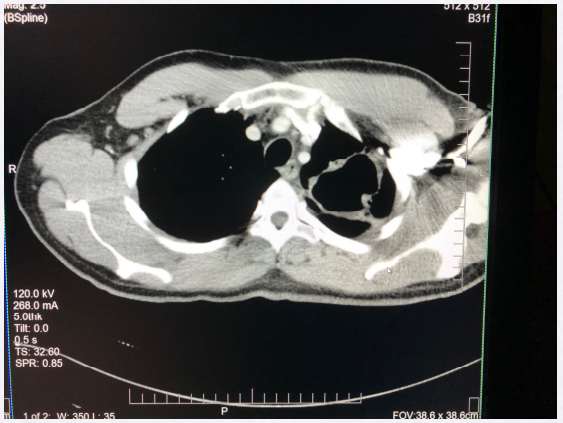
The finding of innumerable tiny cavities would be **<u>Atypical</u>** of TB.

What CT Finding would cause you to question the diagnosis of TB ?



4/8/19 14:07 Tissue - Lung-Left Upper Lobe Complete	Fungal Culture - Final Aspergillus Fumigatus Acid Fast Bacilli Smear - Final Acid Fast Bacilli Culture - Final
4/8/19 14:07 Tissue - Left Upper Lobe Complete	Anaerobic Culture - Final Aspergillus Fumigatus

What is the Radiographic Clue Here that It Might NOT be TB ?



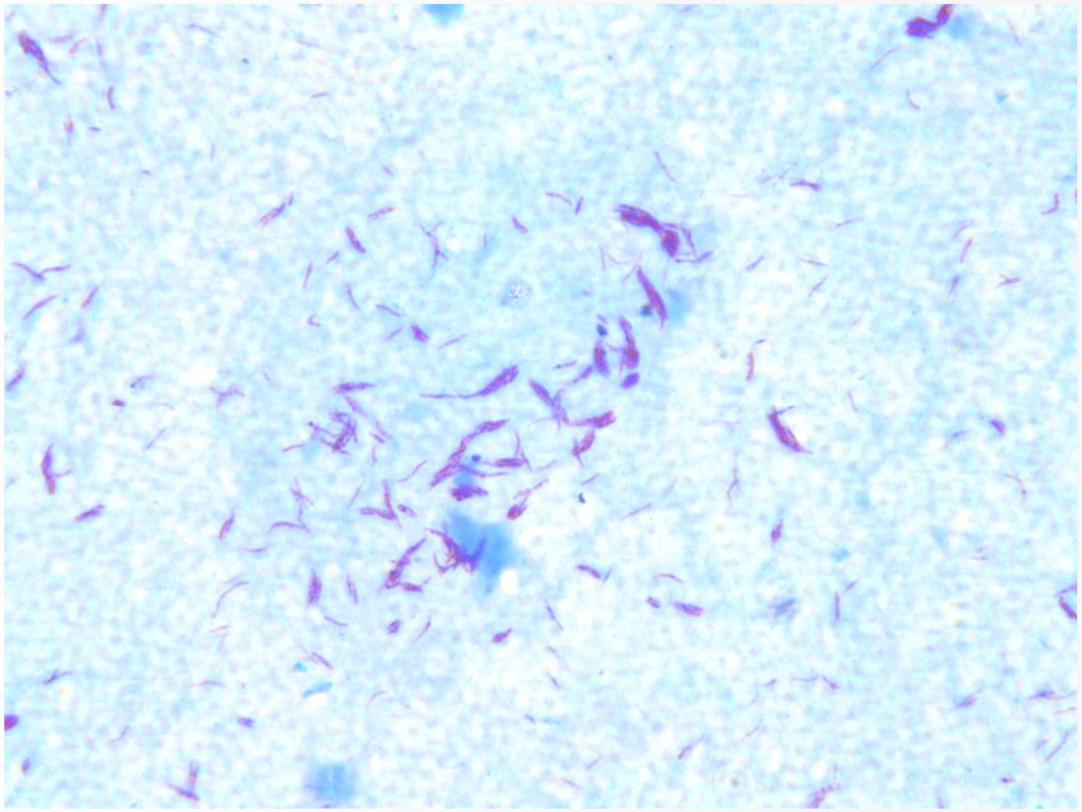
DIFFERENTIAL DIAGNOSIS OF CAVITARY LUNG LESIONS

- Anaerobic lung abscess
- Fungus ball, perhaps in a pre-existing cavity.
- Necrotizing pneumonia due to a drug resistant bacterial pathogen (Pseudomonas, Acinetobacter, Staph aureus).
- Other fungal infections such as Blasto or Histo.

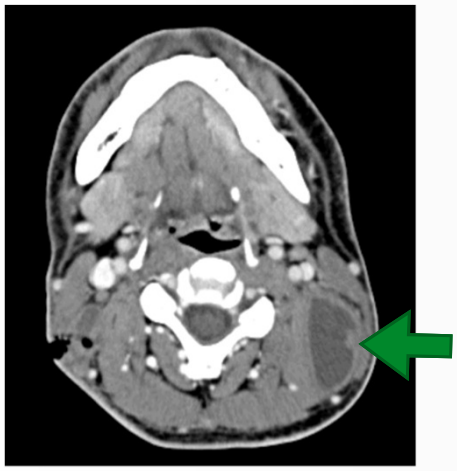
- Emphysematous Blebs
- ANCA + vasculitides such as Granulomatosis with polyangiitis (GPA, "Wegener's"). See recent Grand Rounds by Dr. Alberto Monegro.

M. TUBERCULOSIS

M. tuberculosis **is long and slender, often beaded, and the bacteria adhere to one another in ropy structures, called "cording."**



EXTRA PULMONARY TB- NOT SO RARE



Lymph Node TB

In a 24 y.o. man from Burma

Lymph Node TB

In a toddler from Burma.

Her father had been diagnosed with active TB (pulmonary + Pott's disease of spine).

EXTRA PULMONARY TB

Tuberculous lymphadenitis of cervical lymph nodes; this woman had worked as a hospital pharmacist in her home country in Asia for many years

Tuberculous Lymphadenitis- the most common manifestation of Extra-Pulmonary TB

After 6 weeks of therapy, she had increased swelling and drainage from the biopsy site.

IMAGES IN CLINICAL MEDICINE

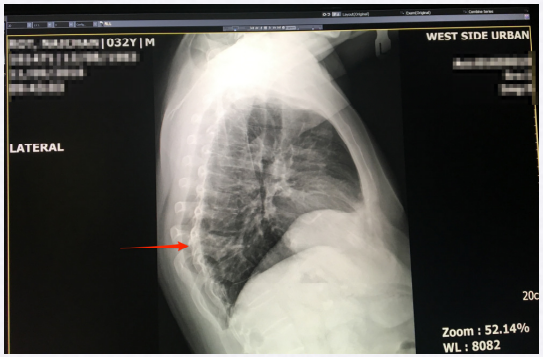
Paradoxical Reaction in the Treatment of Scrofula

Kuan-Chung Ting, M.D., and Gwo-Shu Wang, M.D.

October 29, 2020
N Engl J Med 2020; 383:1767
DOI: 10.1056/NEJMicm2001912
Metrics

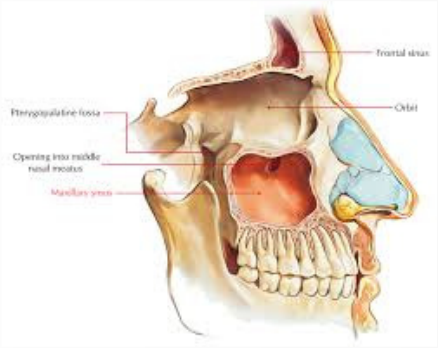
EXTRA PULMONARY TB- SPINE

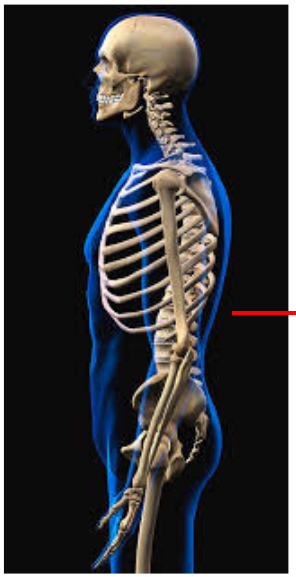
TB of
the Spine,
aka
Pott's
Disease,
in a man
from Burma



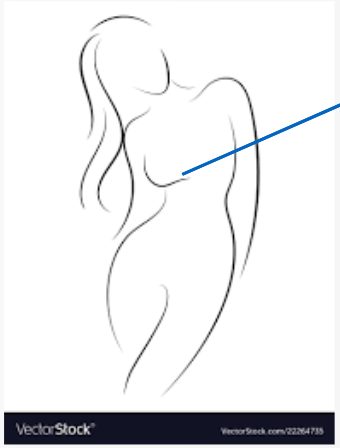
EXTRAPULMONARY TB CASES SEEN IN BUFFALO

TB of the maxillary sinus and upper jaw

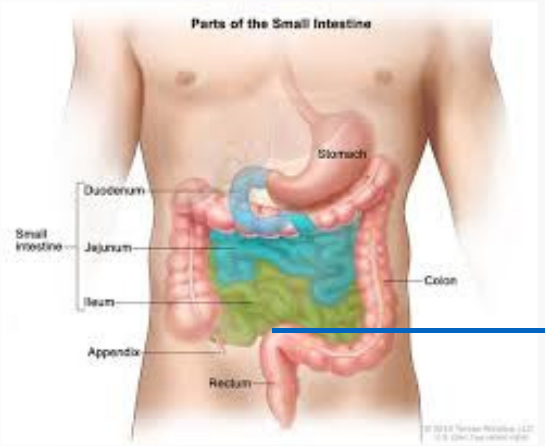




TB of the spine



TB mastitis



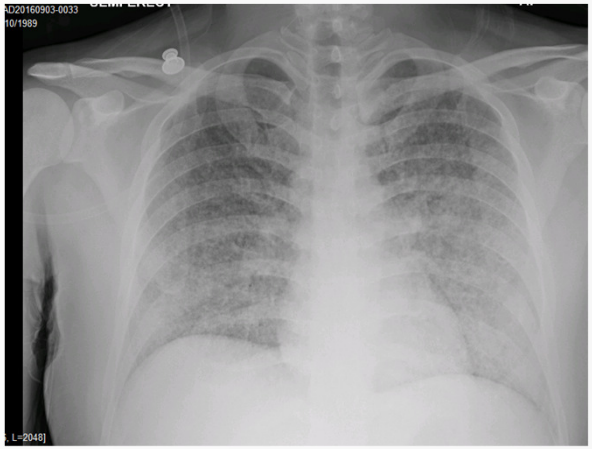
Tuberculous ileitis misdiagnosed as Crohn's disease

MILIARY TB

Miliary TB in a Prisoner

In miliary TB, the lesions are small, nodular, 3- 4 mm, and ALL the SAME SIZE

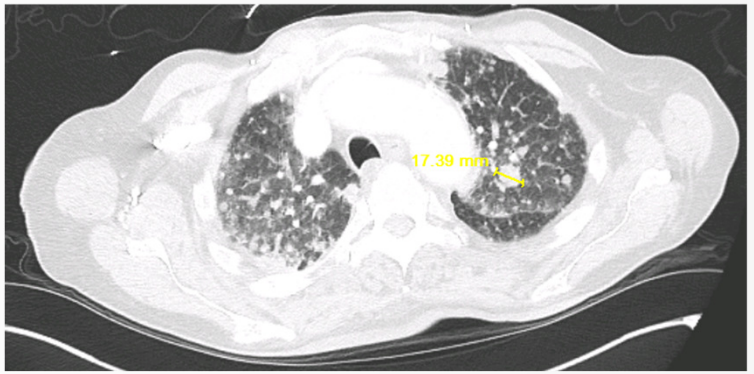
MILIARY TB



CXR showing Miliary TB in a man with Idiopathic CD4 Lymphocytopenia Syndrome; Miliary TB is characterized by 3- 4 mm nodules-

Chest CT
Scan on
the patient
shown
in the previous
CXR.

Not miliary TB

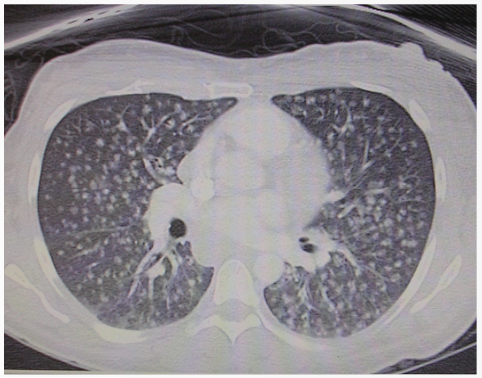


Lesions up to 1.8 cm in size.

Diagnosis was metastatic adenocarcinoma of unknown primary; Liver and Spleen also had mets.

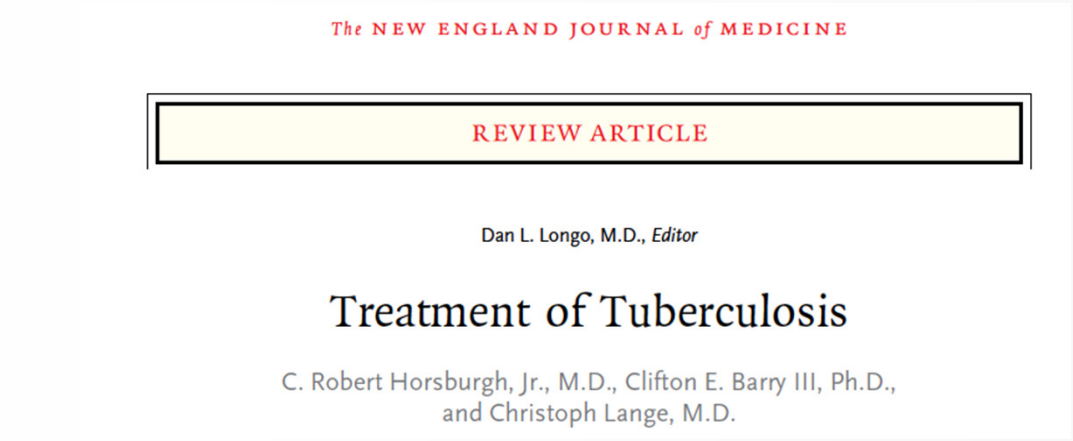
A mimic of miliary TB

Infection with *Mycobacterium avium* with Immune Reconstitution Syndrome after starting ART
4 weeks earlier.



TREATMENT OF ACTIVE TB

- Treatment of Non-MDR TB is **not** that difficult.



- In the average, standard patient being treated for TB for the first time, and **not** a contact of a MDR-TB case, treat with 4 drugs.
  - Standard regimen consists of isoniazid, rifampin, Pyrazinamide, and ethambutol,
  - Plus Vit. B6 while on isoniazid.
  - This regimen is referred to as "RIPE" in most U.S. states and "HRZE" by the WHO

TREATMENT OF ACTIVE TB

- Treatment of TB is “Easy” compared to regimens for some of the non-TB Mycobacteria. Why ?
  - Phenotypic susceptibility testing is reliable and standardized.
  - Genotypic testing is now also very helpful and much quicker in producing results. Gene probes can now detect mutations that predict drug resistance.
  - Examples: *rpoB* mutations predict resistance to rifampin quite reliably.
  - Mutations in *katG* and *inhA* genes predict isoniazid resistance.

ANTI-TB DRUGS

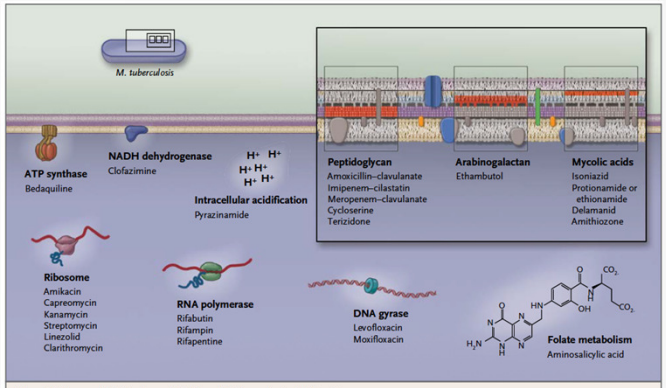


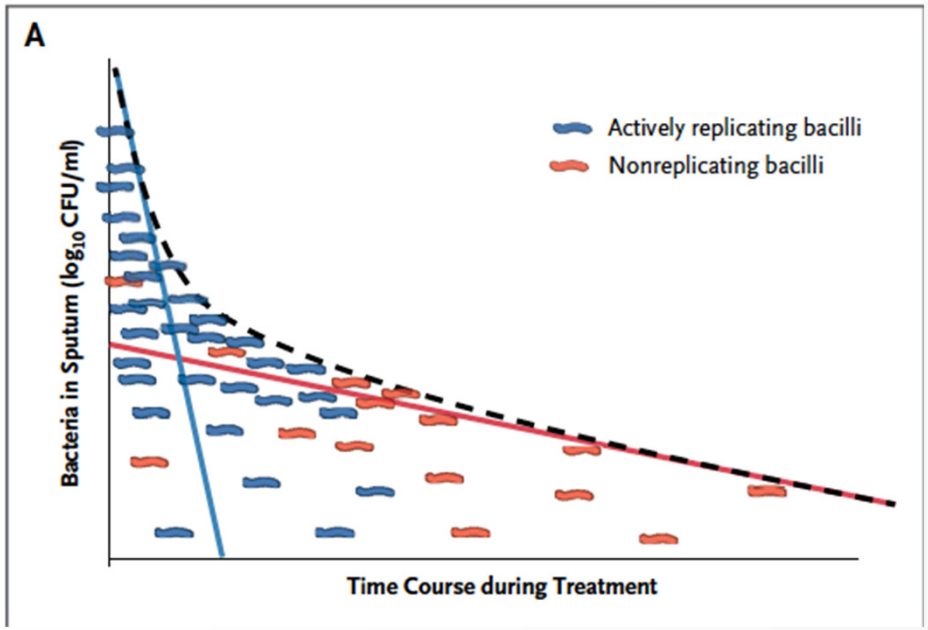
Figure 3. Sites and Mechanisms of Action of Antimycobacterial Agents.

Shown are the known targets of various agents that have been used clinically in tuberculosis treatment. Many antituberculosis agents target the *M. tuberculosis* cell envelope. The box is a high-resolution representation showing the agents that act on each of the three component polymers of the macromolecular outer cell envelope. Drugs such as aminosalicylic acid act like antimetabolites; they are incorporated into folate metabolism as substrates and inhibit downstream folate-dependent processes. The mode of action of pyrazinamide remains enigmatic, and the drug appears to act at least partially by acidifying the cytoplasm of the cell.

2ND-LINE ANTI-TB DRUGS

- Linezolid
- Newer Quinolones; Moxifloxacin & Levofloxacin (not ciprofloxacin).
- Recommended now instead of older 2nd –line drugs such as ethionamide, para-amino-salicylic acid (PAS), or cycloserine.
- IV amikacin is still active against most strains of TB and is a good choice to include in hospitalized patients requiring IV therapy.

BRIEF PATHOGENESIS OF TB TREATMENT



Treatment of Tuberculosis

C. Robert Horsburgh, Jr., M.D., Clifton E. Barry III, Ph.D., and Christoph Lange, M.D.

NEJM. Nov. 26, 2015

LATENT TB: CDC NO LONGER REQUIRES ANNUAL TB TESTING FOR HEALTH CARE WORKERS

Newly Hired Foreign Born

Yes

They will test.

Participated in an International Mission Trip to a High TB-Incidence Country

Yes

They will test.

Taking a Biologic Agent such as a TNF Antagonist or Immunosuppression

Yes.

Received Treatment for Cancer

HOW TO TEST FOR LATENT TB

Tuberculin skin test (PPD)

- Tried and true
- Requires reading at 48- 72 h
- Easier to do if you have very large numbers of people to test, like in an outbreak at a school
- Requires an experienced reader- induration is what counts.
- Hard to find the results in the EMR.
- Costs about $ 4
- About 70 -75% sensitive in active TB
- Nationwide shortage of Aplisol® and Tubersol® in the US, 2019

Interferon-Gamma Release Assays

- QuantiFERON test or
- T-SPOT TB- newer, more technically challenging, and not widely used in the U.S.
- **Doesn't cross-react with previous BCG vaccination.**
- More variable from test to test on the same individual - relies more on the physiologic state of the immune system at the time the specimen is drawn.
- Costs about $ 170.
- About 75 -85% sensitive in active TB
- Indeterminate does not mean "Intermediate"

- If you don’t test everyone in your hospital, who do you test for TB ?

DRUG REGIMENS FOR LATENT TB

—— ACTIVE TB EXCLUDED——

Isoniazid for 9 months

Preferred regimen for children 2 to 11 years old.

Least expensive.

Give with Vitamin B6, of course.

Isoniazid + Rifapentine Weekly x 12 doses

Not for children under 2

Not a good choice for people with HIV taking a PI-based ART regimen.

Not recommended for pregnant women.

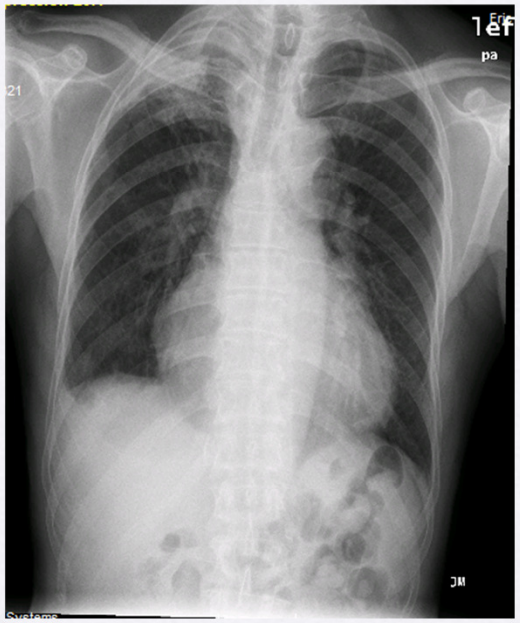
Rifampin daily x 4 months

Check drug interactions.

Not good for some ART regimens.

CASE- DIAGNOSTIC CHALLENGE

- An 85 year old man, originally from Vietnam, presented to the ECMC Emergency Room because of minor hemoptysis.
- He also had cough and sputum production, but no fever .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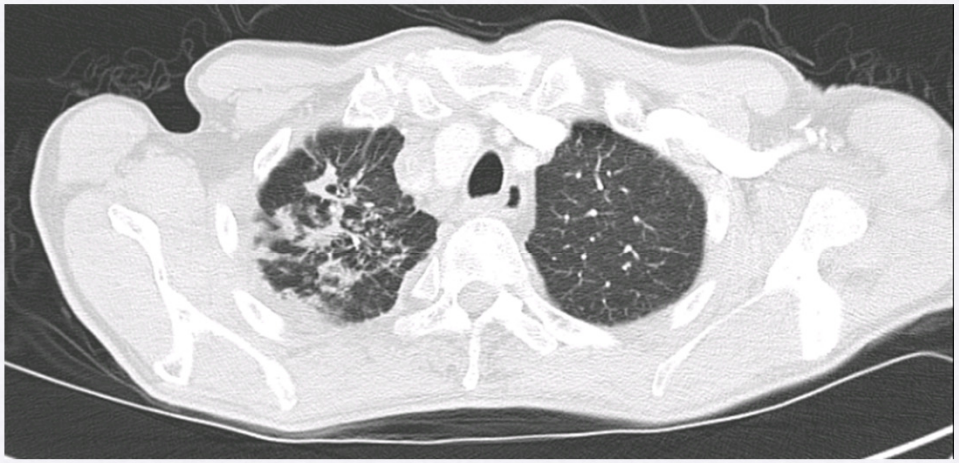
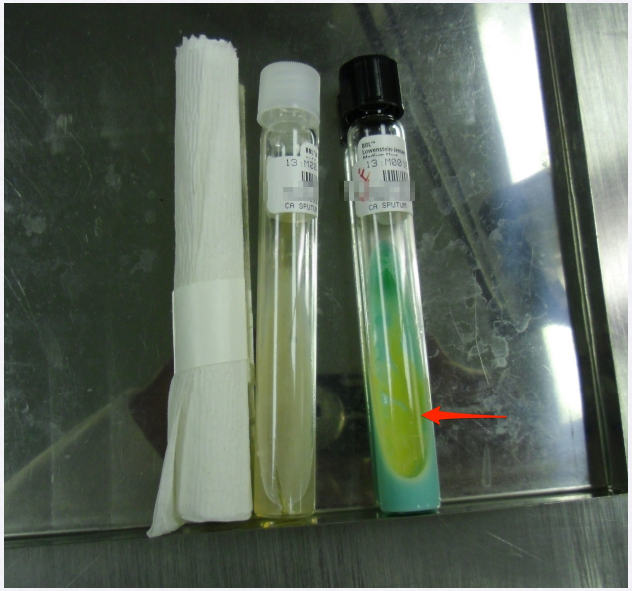


He was started on anti-TB drugs, and referred to TB Clinic

Sputum cultures turned positive, But gene probe testing of the sputum isolate was (-) for
M. tb complex, *M. gordonae*, and *M. avium*. Growth on Lowenstein-Jensen solid medium showed the following:



What are the diagnostic possibilities ?

M. marinum and *M. kansasii* are the 2 classic photochromogens.

7/3/14 08:35 Sputum Complete	Acid Fast Bacilli Smear - Final Acid Fast Bacilli Culture - Final Mycobacterium Asiaticum
7/2/14 08:00 Sputum Complete	Acid Fast Bacilli Smear - Final Acid Fast Bacilli Culture - Final Mycobacterium Asiaticum
7/1/14 21:39 Sputum Complete	Acid Fast Bacilli Smear - Final Acid Fast Bacilli Culture - Final Mycobacterium Asiaticum

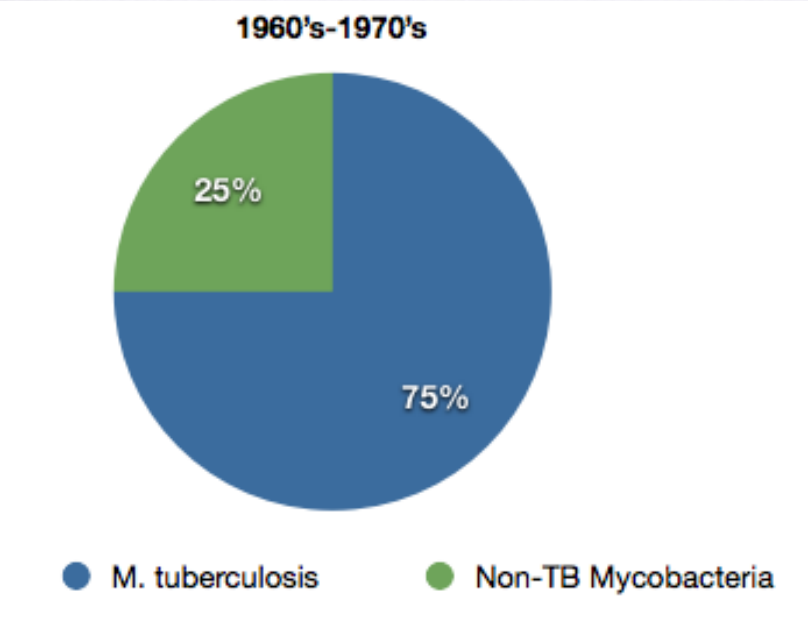
Be prepared
to see names of
mycobacteria
that you have
never heard of.
Do a Lit. Search
or Up-to-Date search

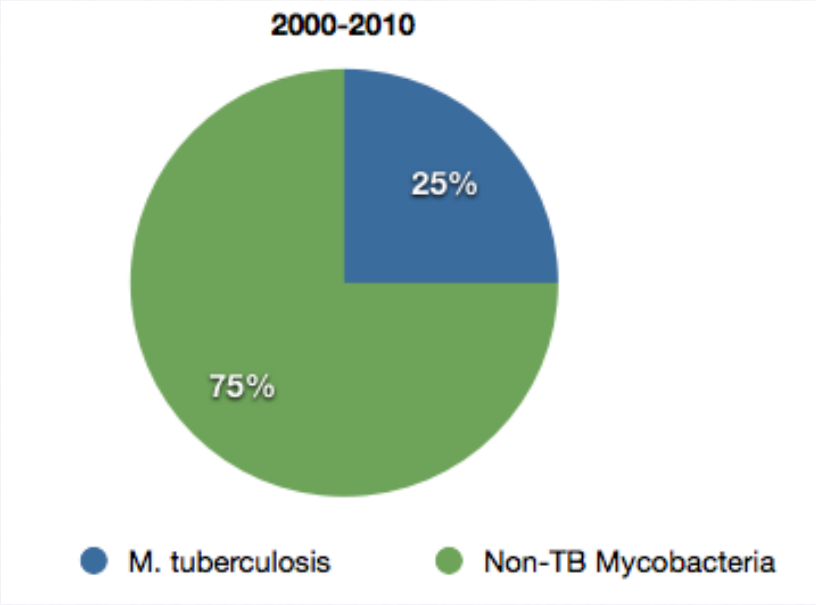
NON-TB MYCOBACTERIAL INFECTIONS

174 species of non-TB mycobacteria now recognized.

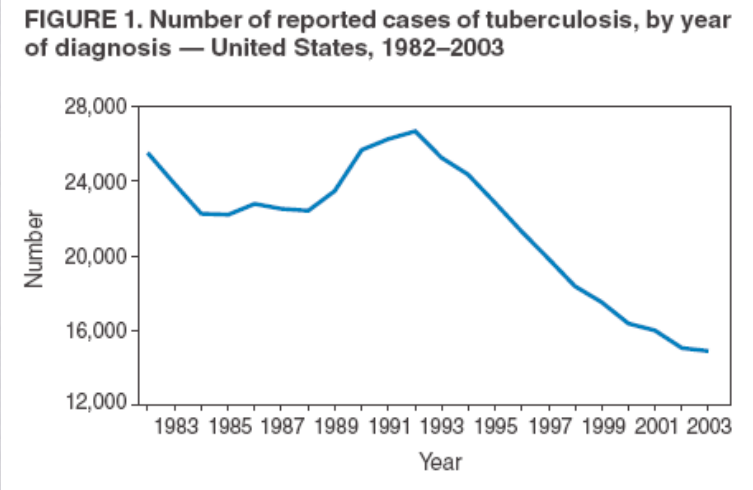
- Many new species being discovered.
- Old species are being re-classified due to DNA sequencing.
- Progress is slower on understanding the environmental sources of these mycobacteria and their significance.
- As an example, *Mycobacterium smegmatis* has 1150 different types of bacteriophages that use it as a host.

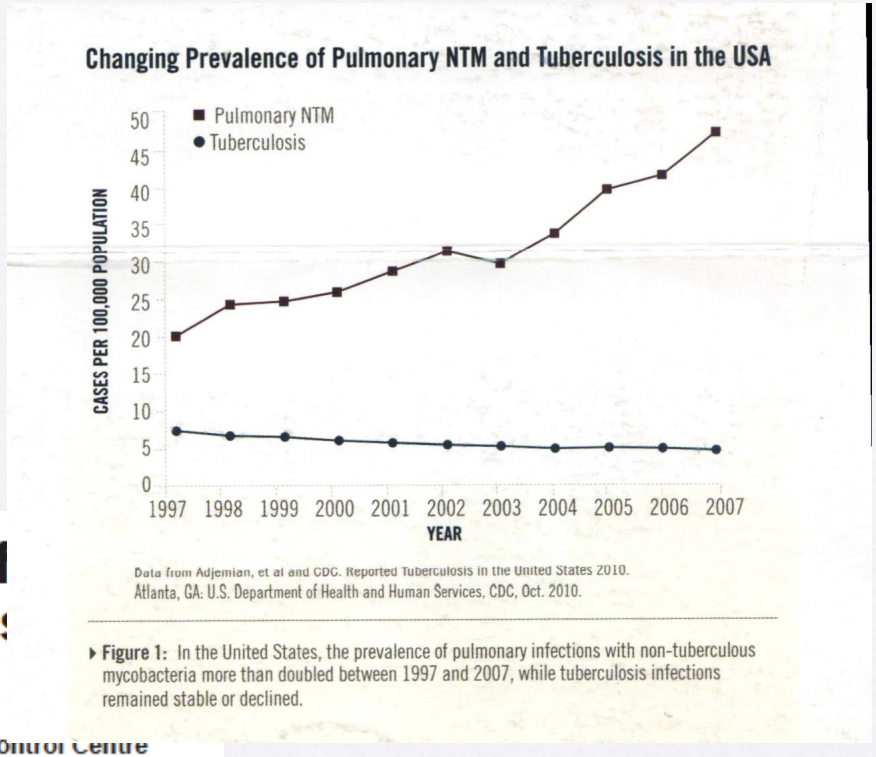
Changing Epidemiology of Mycobacterial Infections





Trends in Mycobacterial Infections





Changing Epidemiology of Pulmonary Nontuberculous Mycobacteria Infections

Rachel M. Thomson, on behalf of the NTM working group at the Queensland TB Control Centre and Queensland Mycobacterial Reference Laboratory

On most continents of the world, TB incidence is declining while incidence of non-TB lung infections is increasing

Why the Increase?

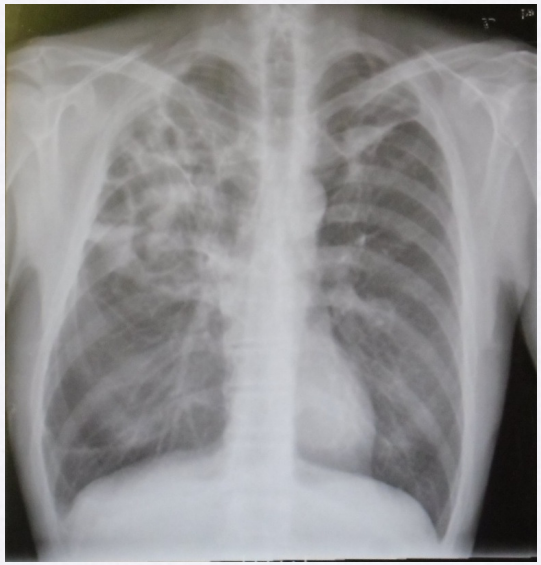
- No one knows for sure
- NOT due to HIV/AIDS
- Preceded the availability of anti-TNF therapies for inflammatory bowel disease and rheumatoid arthritis; anti-TNF treatments such as infliximab and etanercept increase the risk of non-TB mycobacteria as well as of TB.
- Theories relate to the common finding of Mycobacteria in municipal drinking water and home plumbing.

3 Classic Clinical Forms of Non-TB Mycobacterial Infection of the Lung

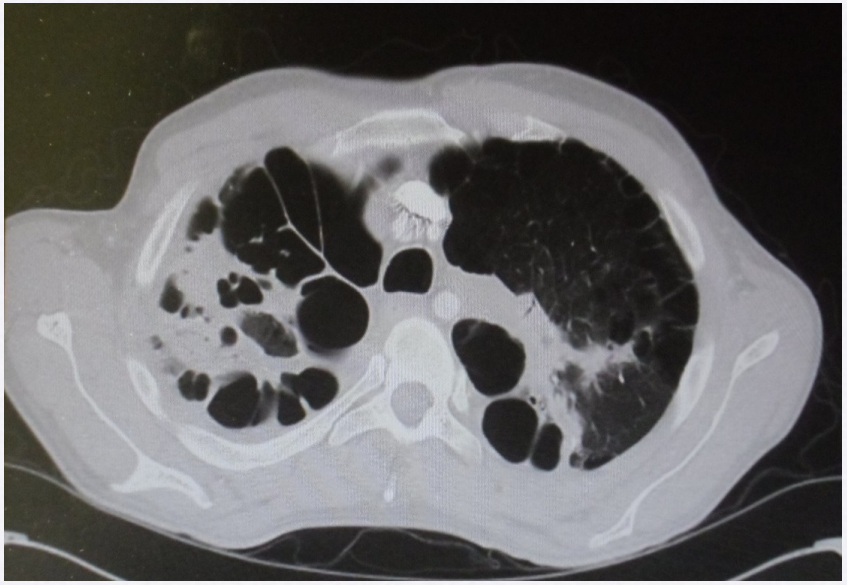
Fibro-cavitary form	Men with COPD or occupational lung disease
Nodular-bronchiectatic form	Thin older white women non-smokers "Lady Windermere syndome"
Hypersensitivity pneumonitis, Hot-Tub lung	users of jacuzzis, spas

Fibro-cavitary form

48 y.o. man, laborer from Buffalo, long-time smoker, adm to County Hospital



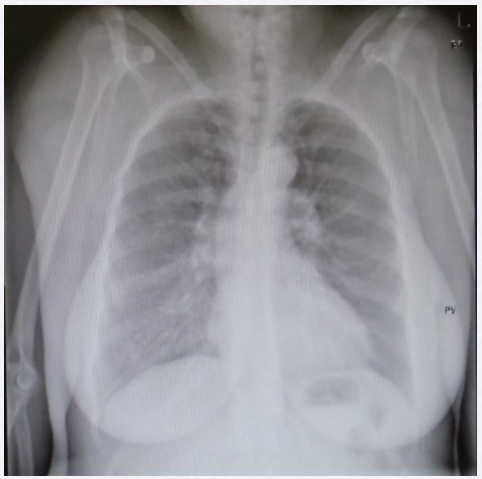
Fibro-cavitary form; CT scan from same pt.



Sputum smears were (-), but grew ***M. avium*** complex on 2 separate specimens

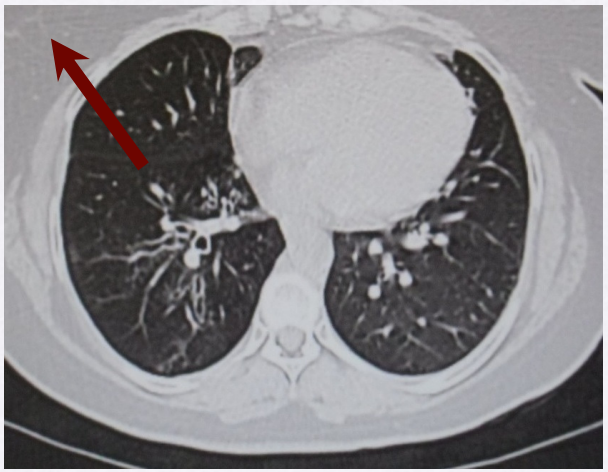
Nodular-Bronchiectatic Form

44 y.o.
woman adm.
to ECMC;
CXR showed
interstitial markings and
small
nodules



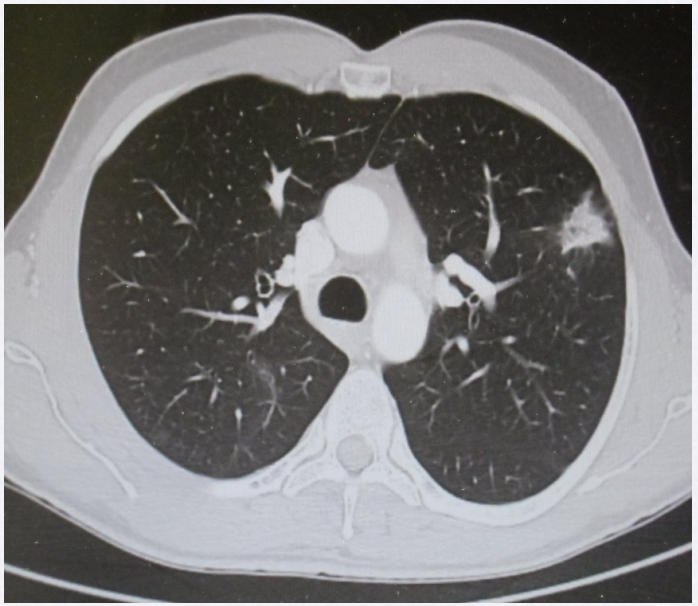
Named “Lady Windermere syndrome, “ based on “Lady Windermere’s Fan,” by Oscar Wilde.

Nodular-Bronchiectatic Form



Nodular-Bronchiectatic Form in a 47 y.o. man, prisoner.

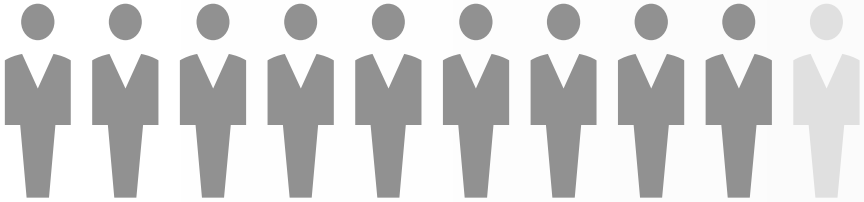
Lord Windermere's syndome?



NON-TB MYCOBACTERIAL STATISTICS

TB

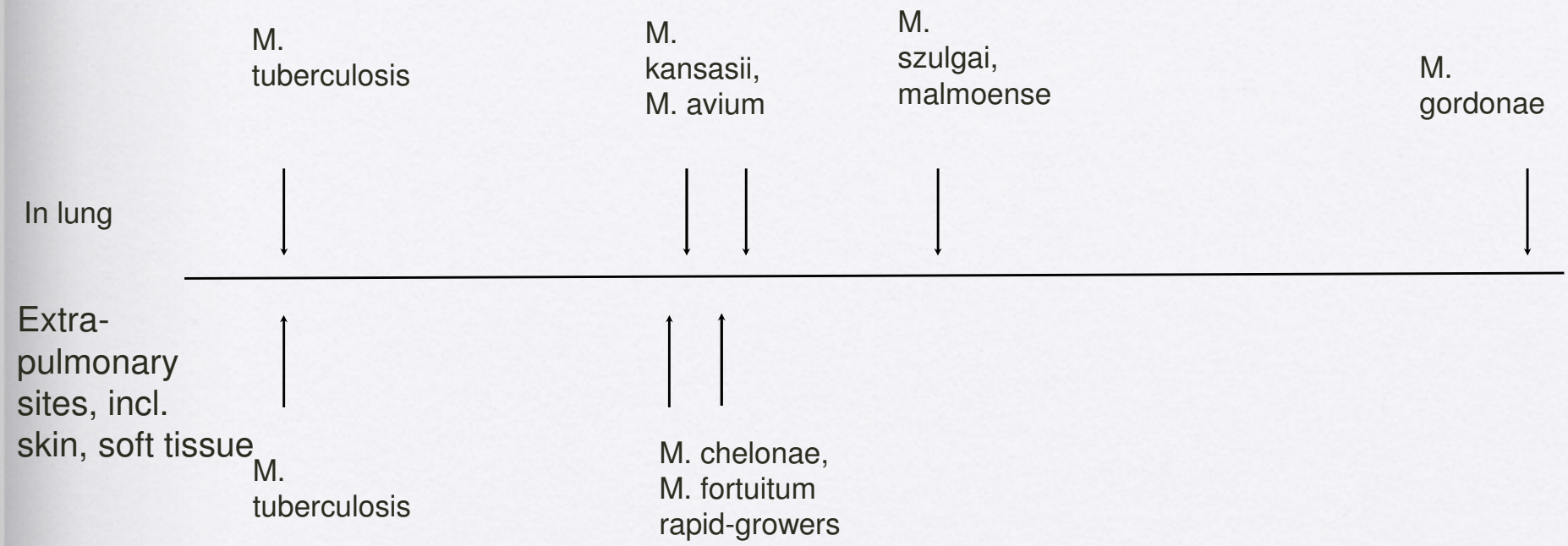
Since Non-TB Mycobacterial Infections are not reportable diseases, accurate statistics are harder to come by than for TB.



67 X non-TB Myco

In Florida among Medicare patients, **Administrative Data** (Billing Codes) indicates that **Pulmonary Non-tuberculous mycobacterial** infections are **67 times more common** than cases of TB.

Spectrum of Virulence/Pathogenicity of Selected Mycobacteria



New species of mycobacteria are being discovered on a regular basis !

TREATING NON-TB MYCOBACTERIAL INFECTIONS

Often harder than treating TB. Long, grueling treatment courses. High incidence of Re-infection with a new strain, even if treatment succeeds.

	TB	M. kansasii	M. avium complex
Susceptibility Testing	**reliable**	**reliable; M. kansasii resistant to PZA; rifampin susceptibility most important**	Testing **only validated for macrolides & amikacin**

TREATING NON-TB MYCOBACTERIAL INFECTIONS

Daley CL, Iaccarino Jr JM, Lange C, Cambau E, Wallace RJ, Andrejak C, Böttger EC, Brozek J, Griffith DE, Guglielmetti L, Huitt GA. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline: executive summary. Clinical Infectious Diseases. 2020 Aug 14;71(4):e1-36.

2020

Charles "Chuck" Daley, National Jewish Health

Richard J. Wallace, Tyler, TX

Gwen Huitt, National Jewish Health

QUESTION 1

- A patient in your practice who is a Physicians's Assistant asks to have a Quantiferon test as required by his employer. There is a shortage of PPD reagent so he cannot get a PPD.
- The Quantiferon test comes back Positive. He does not have symptoms suggesting active TB.

- Which of the options is the correct next follow-up step for this health-care worker ?

- A. Inform the Health Department and the patient that all of his close family contacts must come in for Chest X-rays
- B. Obtain a Chest X-ray on the health-care worker
- C. Begin isoniazid for 4 months, plus Vitamin B6
- D. Inform the health-care worker that the test is a false positive due to his previous receipt of the BCG vaccine.

QUESTION 2

- According to the CDC, the population group that accounts for the largest proportion of cases of active TB in the United States consists of:

- A. People who have served time in jail or prison
- B. Patients with HIV
- C. Patients with cancer
- D. People born in foreign countries with a high incidence of TB
- E. People who reside in or have visited Florida.

QUESTION 3

- A patient with rheumatoid arthritis is tested by the Rheumatologist's office for TB prior to initiation of therapy with a tumor necrosis factor (TNF) inhibitor for the arthritis. The Quantiferon test is Positive. The patient is well, except for her joints, and a CXR is normal . Which of the following is an appropriate treatment for this patient?

- A. Isoniazid (INH) 300 mg po daily plus Vitamin B_6 for 9 months.
- B. Begin 4-drug therapy for TB, consisting of INH, rifampin, pyrazinamide (PZA), and ethambutol, plus Vitamin B_6.
- C. Rifampin 600 mg po daily plus Vitamin B_6, for 9 months.
- D. Isoniazid plus Rifapentine monthly x 9 months.