

Le infezioni da micobatteri: nemici dimenticati ma difficili

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Conflicts of interest

- No conflicts of interest to disclose

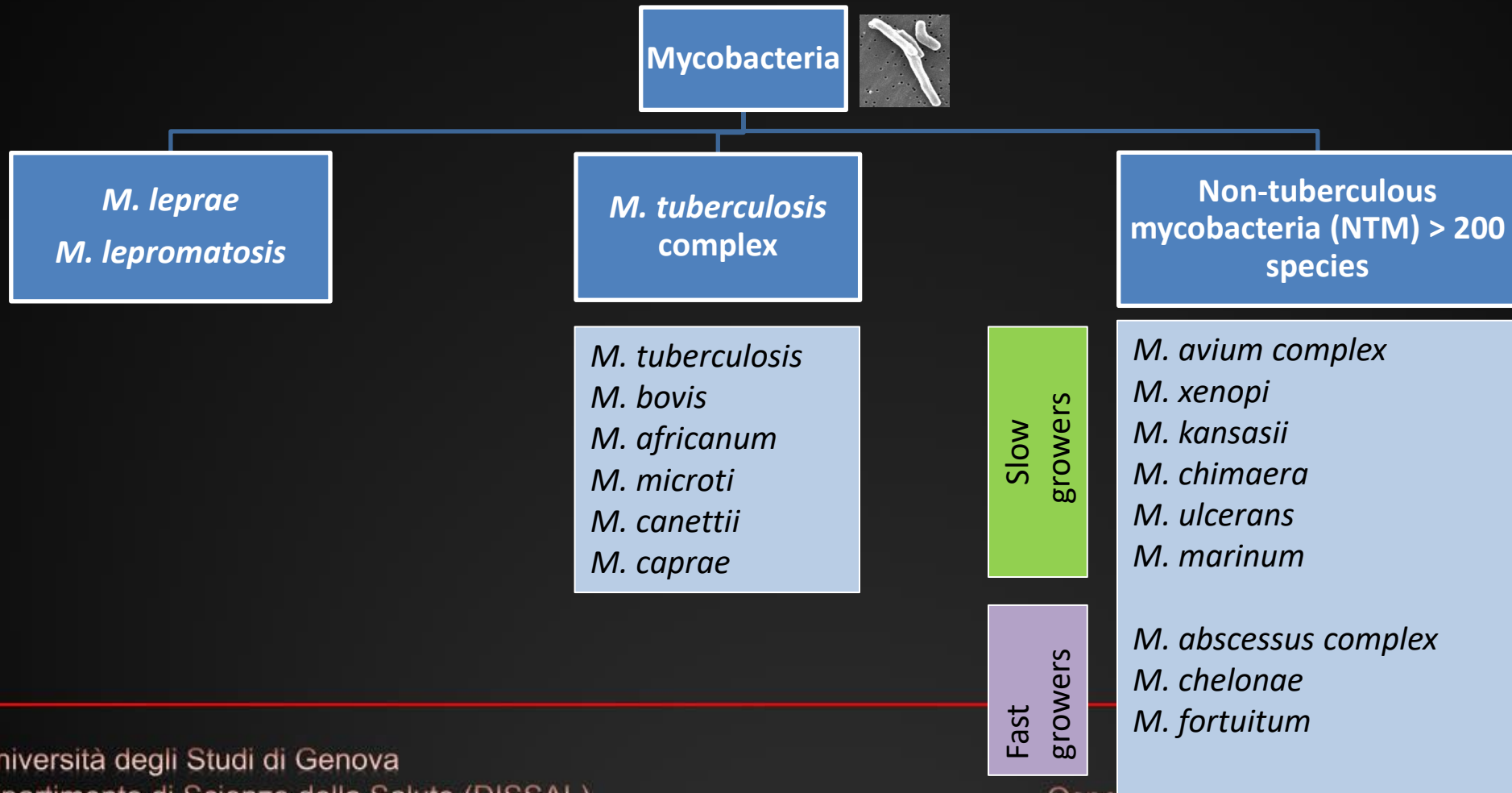


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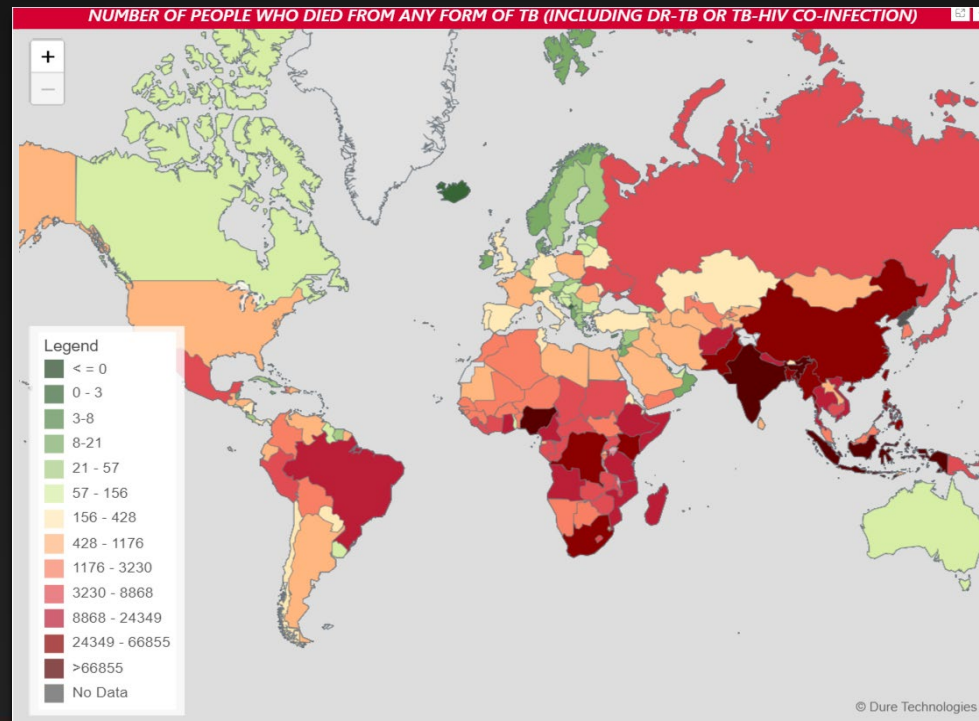
WHICH MYCOBACTERIA? MYCOBACTERIA OF CLINICAL SIGNIFICANCE



TUBERCULOSIS – DISEASE BURDEN

World's top infectious killer

In 2022: 10.6 million cases worldwide (1.3 million children), 1.3 millions deaths, 2 million missed diagnosis
410 000 cases of MDR-TB, only about 2 in 5 accessed treatment



<https://dashboards.stoptb.org/map-dashboard.html>



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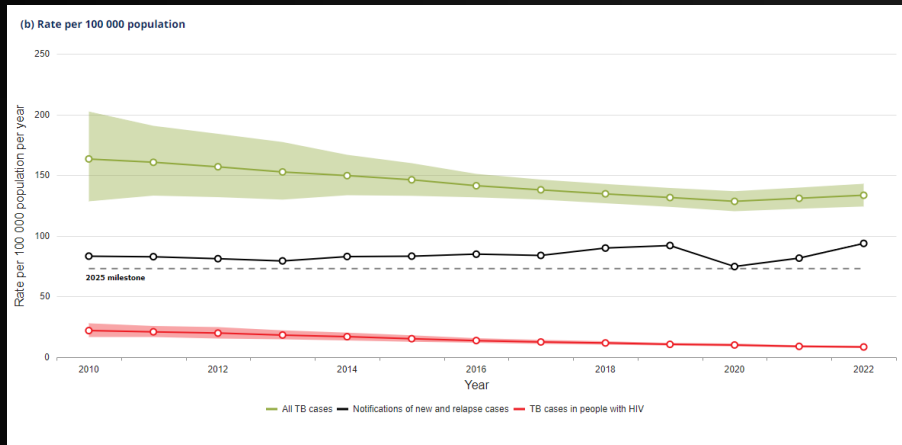
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TUBERCULOSIS – DISEASE BURDEN

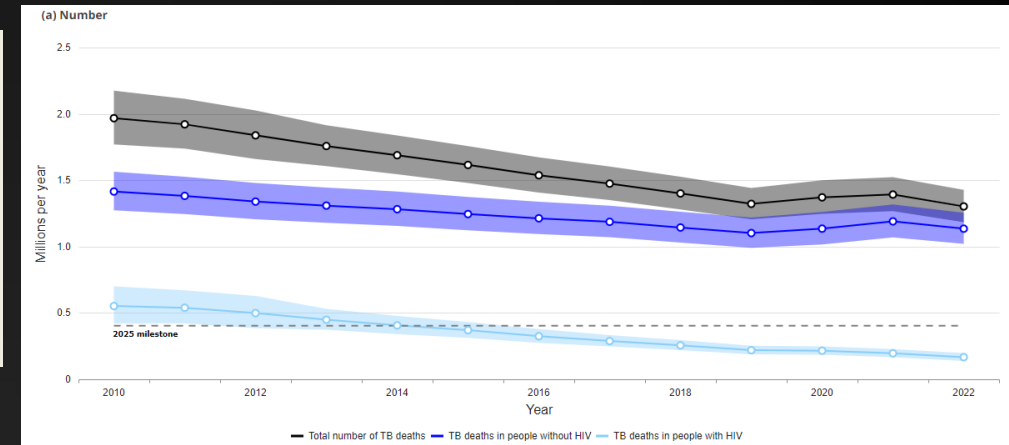
Did we reach the endTB strategy goals?

TB incidence worldwide



Disruptions during the COVID-19 pandemic and its aftermath are estimated to have resulted in close to half a million excess deaths from TB in the three years 2020–2022

TB mortality worldwide



Actions needed: scale up diagnostic and care, prevention, accelerate development of new tools, mobilize funding.
(Total funding gaps reported in 2022 amount to US\$ 1.5 billion)

WHO Global Tuberculosis Report 2023

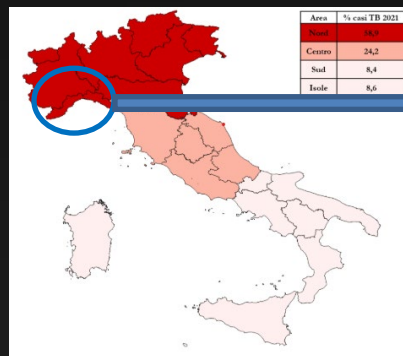
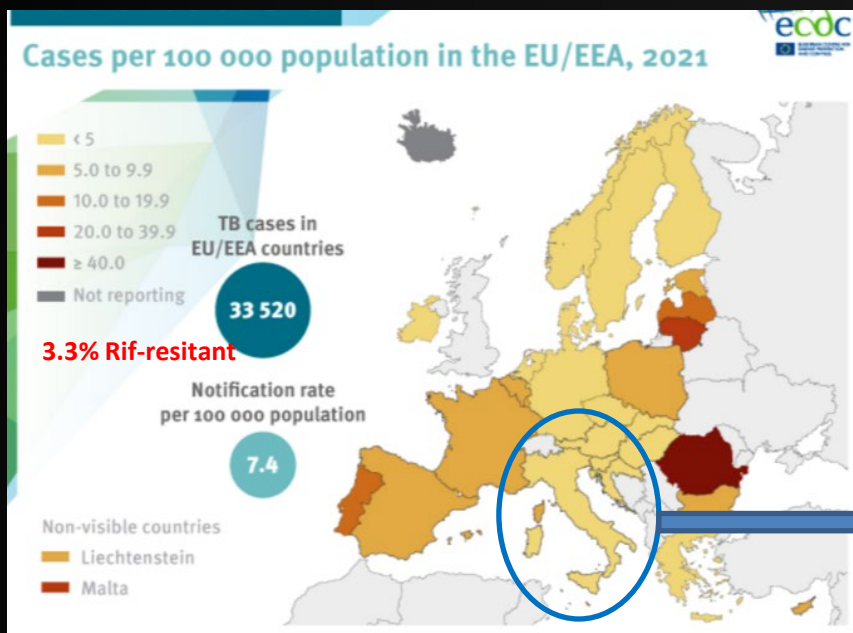


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TUBERCULOSIS – DISEASE BURDEN in Europe and Italy



Popolazione italiana 5 casi /100.000 abitanti
Popolazione straniera 60 casi/100.000 abitanti (dati 2018)

In 2021: 2480 cases
Foreign-born 57.9%
Mean age native: 54 years
Mean age foreign born: 38 years

Actions needed for key population (migrants)

- active case finding
- increase access to healthcare system
- retention in care and follow-up

Tuberculosis surveillance and monitoring in Europe 2023- 2021 data – ECDC

REGIONE LIGURIA Piano Regionale della Prevenzione 2014-2018

Linee guida salute migranti, 2024 - Il controllo della tubercolosi tra gli immigrati in Italia (INMP,ISS;SIMM)

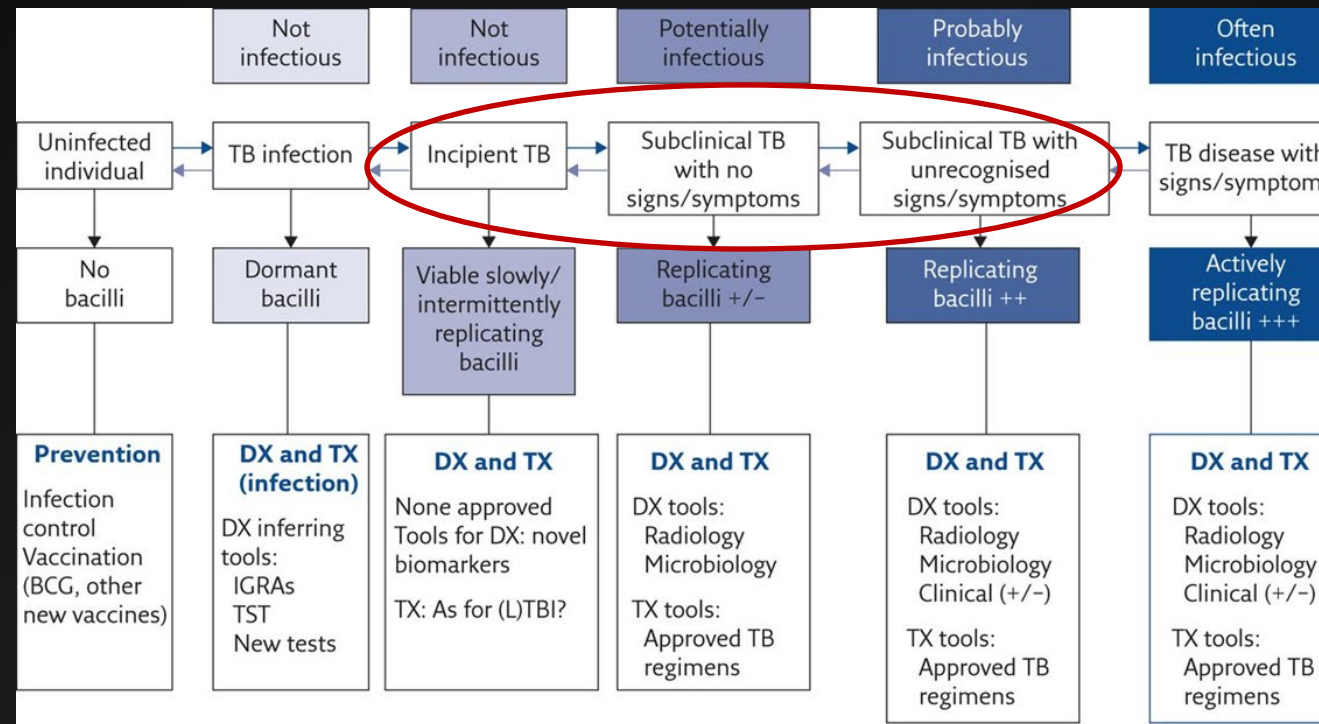


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TUBERCULOSIS – FROM INFECTION TO DISEASE



Current diagnostics can only detect TB infection and active TB. Biomarkers able to identify incipient and subclinical TB and risk factors for progression to active TB are needed.

Drain PK et al (2018), *Clin Microbiol Rev* 31:e00021
Migliori GB et al (2021), *Breathe* 17:210079



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TUBERCULOSIS –DIAGNOSIS OF ACTIVE TB

Routine investigations for tuberculosis on bronchoalveolar fluid lavage in a low-incidence setting: is it worth it?

Chiara Sepulcri , Ramona Barbieri , Lorenzo Crupi, Maria Bonaffini , Emanuele Delfino , Elena Tagliabue , Antonio Di Biagio, Emanuela Barisione , Anna Marchese, Matteo Bassetti

• METHODS

Routine Xpert Ultra + culture + microscopy performed on every BALF performed in the bronchoscopy unit since 2018. Retrospective analysis assessing the rate of TB diagnosis (Xpert Ultra result as the index test) and the number of cases in which TB was not suspected.

• RESULTS

1694 BALF samples were investigated for TB, n=47(2.8%) Xpert Ultra positive.

n=40(85%) were requested due to a TB suspect.

In seven cases, there was no clear TB suspect at the time of bronchoscopy (0.4% of all bronchoscopies performed without TB suspect).

All patients but one were Italian-born, mean age was 75.5 years (SD 9.5).

Case	Reason for admission and bronchoscopy	Presence of typical symptoms (cough, night sweats, fever)	Radiological features	TB culture on BALF	Outcome
#1 Female, 91 yo Italian	Respiratory failure with new pulmonary infiltrates in suspected laryngeal malignancy	No	Lingular consolidation, bilateral pleural effusion	Positive	Treatment completed
#2 Male, 76 yo Italian	Incidental finding of pulmonary infiltrates in pre-operative CT scan for hip replacement	No	Left upper lobe consolidation	Positive	Treatment completed
#3 Male, 66 yo Foreign-born	Acute symptom onset (fever and dyspnea) after recent stroke and COVID-19 with steroid administration	Fever, cough	Diffused ground glass opacities, consolidation left upper lobe	Positive	Treatment completed
#4 Male, 75 yo Italian	Dysphagia and cough with pulmonary infiltrates in patient undergoing chemotherapy for pancreatic malignancy suspect for <i>P. jirovecii</i> pneumonia	No	Ground glass bilateral infiltrates	Negative	Lost-to-follow-up (COVID-19 pandemic)
#5 Male, 65 yo Italian	Pulmonary nodules in follow-up for suspected malignancy in heavy-smoker	No	Left upper and lower lobe consolidation, mediastinal lymphadenopathies	Positive	Treatment completed
#6 Male, 79 yo Italian	Plural effusion, respiratory failure and bilateral nodularities in patient on hemodialysis	No	Micronodular infiltrates bilaterally, pleural effusion, mediastinal lymphadenopathies	Positive	Death 24 days after treatment initiation
#7 Male, 76 yo Italian	Pulmonary nodules in follow-up with FDG uptake, asbestos exposure	No	Middle right lobe consolidation, bilateral micronodules	Positive	Treatment completed



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TUBERCULOSIS –DIAGNOSIS OF ACTIVE TB

SPUTUM BASED METHODS

STANDARD MICROBIOLOGY

- Microscopy
- Culture

PCR

- Xpert (RIF/Ultra/XDR)
- LPA (on culture)

NGS

- Targeted NGS (sputum)
- WGS (culture)

Increased sensitivity, accuracy in resistance detection, evaluation of lineage

NON-SPUTUM BASED METHODS

- Urinary LAM
- Stool Xpert
- Blood? (fingerstick, phages)
- Exhaled Breath Aerosol?

Ease of collection, possible diagnosis of incipient/subclinical TB



TUBERCULOSIS – ADVANCES IN TREATMENT (DS-TB)

CAN WE SHORTEN THE TREATMENT OF PULMONARY DRUG-SUSCEPTIBLE TB?

Currently recommended

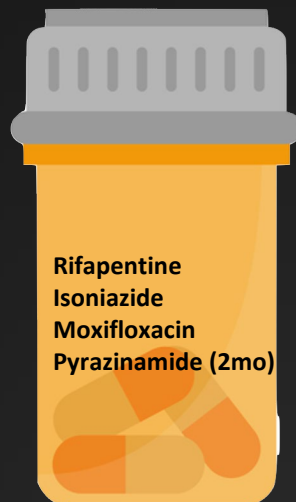
- **6 months 2HRZE/4HR**

Also applies to all forms of extrapulmonary TB except CNS and bone and joint, disseminated

Favourable outcome 85 – 90%

- **4 months 2HPMZ/2HPM**

Only pulmonary TB regardless of severity, > 12 years > 40 kg.
Recommendation based on the results of Study 31



2 months?

TRUNCATE TB, adaptive trial 8 wks of experimental regimen
prolongable if persistence
674 participants, no PLHIV enrolled.

ARM	TREATMENT
Active Comparator	2HRZE/4HR
Regimen B	Rifampicin (35mg/kg), isoniazid, pyrazinamide, ethambutol, linezolid;
Regimen C	Rifampicin (35mg/kg), isoniazid, pyrazinamide, ethambutol, clofazimine;
Regimen D	Rifapentine, isoniazid, pyrazinamide, linezolid, levofloxacin
Regimen E	Isoniazid, pyrazinamide, ethambutol, linezolid, bedaquiline

Non-inferior to standard treatment with shorter treatment duration (median 85 days SD 65)



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WHO consolidated guidelines on tuberculosis: module 2: treatment drug-susceptible TB
Dorman SE; NEJM 2021
Paton NI; NEJM 2023

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TUBERCULOSIS – ADVANCES IN TREATMENT (DS-TB)

ACCESS TO TB TREATMENT



RIFAPENTINE: never filed for registration to EMA

RIFAMPICIN: shortage: **recurring and worrisome issue**

Actions needed: define the extent of the problem (scientific societies), advocacy

Guglielmetti Li; ERJ 2022



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TUBERCULOSIS –TREATMENT of DR-TB

DRUG-RESISTANT TB DEFINITIONS

KNOWING THE TYPE OF RESISTANT IS ESSENTIAL TO GUIDE TREATMENT

Hr-TB=Rifampicin-susceptible, isoniazid-resistant TB

RR-TB=Rifampicin-resistant TB: rifampicin resistant TB

MDR-TB=Multidrug-resistant TB: rifampicin and isoniazid resistant TB

Pre-extensively drug resistant (pre-XDR) TB= rifampicin \pm isoniazide + fluoroquinolone resistant TB (2021)

Extensively drug resistant (XDR) TB = rifampicin \pm isoniazide + fluoroquinolone resistant + bedaquiline or linezolid resistant TB

**WHAT ABOUT INJECTABLES? PROGRESSIVE DE-PRIORITIZATION IN LIGHT OF EFFECTIVE ALL-ORAL REGIMENS
DUE TO ELEVATED ADVERSE EVENTS AND NO CLEAR CLINICAL BENEFIT**

WHO consolidated guidelines on tuberculosis: module 2: treatment drug-resistant TB



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TUBERCULOSIS –TREATMENT of DR-TB

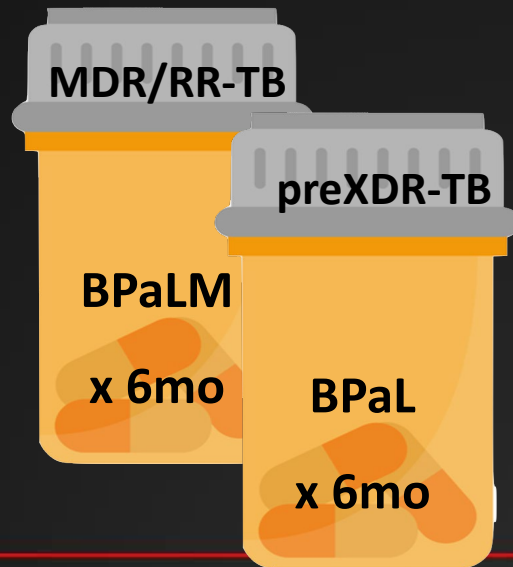
CURRENT and FUTURE TREATMENT OPTIONS

WHERE WE WERE

- Long duration
- (18-20 months)
- Required injections
- Toxicity
- Poor efficacy (≈57%)

Currently recommended treatments

TB-PRACTECAL trial (89% success rate)
ZeNix trial



Future?



Three new BDQ-containing regimens non-inferior to SoC



GSK6562: leucyl-tRNA synthetase inhibitor

BTZ-0433: benzothiazinone, cell wall synthesis inhibitor



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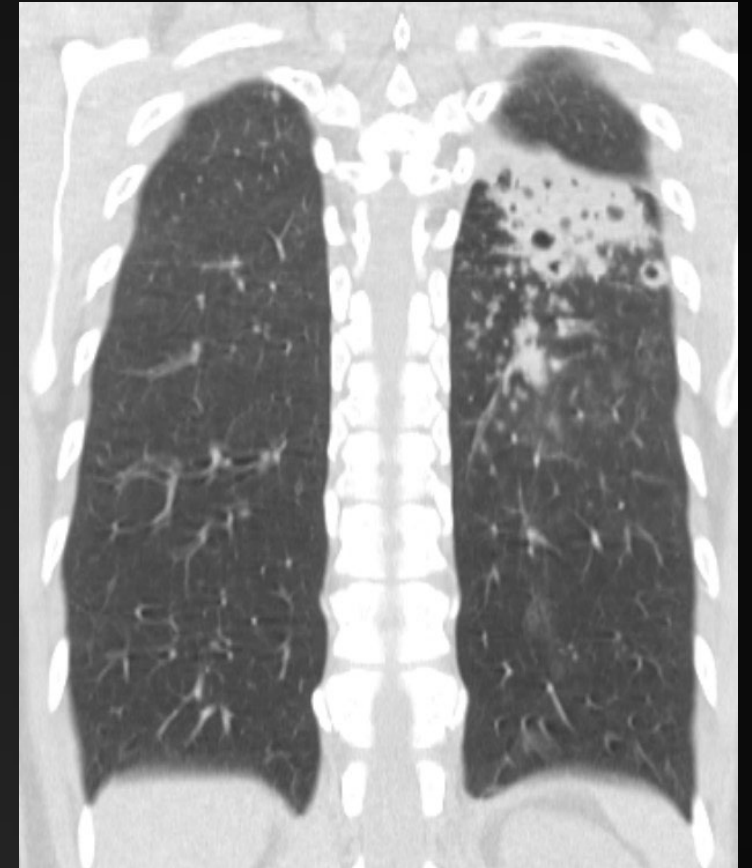
WHO consolidated guidelines on tuberculosis: module 4: treatment drug-resistant TB

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TUBERCULOSIS – CLINICAL CASE

- 32 yo man born in Perù
- Come back to Italy April '24 (he left EU in 2018)
- Since March '24 fever, chills, productive cough with haemoptysis
- Weight loss of 6 Kg in the last months
- Documented CAP by *S. pneumoniae* (urinary antigen +)



TUBERCULOSIS – CLINICAL CASE

- 29/04/24 smear ++ → 30/04/24 HRZE
- 07/05/24 Rapid growing (1 week) with culture + for *M. tuberculosis*
- 08/05/24 PCR pos [**rpoB mutation detected** (Ile 491 Phe)] → **RR TB**
- 09/05/24 transferred to our Department

Which Therapy?

DETERMINAZIONE 1 marzo 2023
Inserimento del regime BPaLM (pretomanid in combinazione con bedaquilina, linezolid e moxifloxacin) nell'elenco istituito, ai sensi della legge 23 dicembre 1996, n. 648, per il trattamento di pazienti, di età maggiore o uguale a quindici anni, affetti da tubercolosi polmonare multifarmacoresistente (MDR), che non hanno avuto una precedente esposizione a bedaquilina, pretomanid e linezolid (definita come esposizione maggiore di un mese).



BPaLM

Indication:

treatment of MDR TB without previous exposure (> 4 weeks) to bedaquiline (B), pretomanid (P) and linezolid (L)

Therapy (24 wks):

- B 400mg/d for 2 wks
→ 200mg/3times/wk
- P 200mg/d
- L 600mg/d
- M 400mg/d

Inclusion criteria:

- Age > 15 yo
- Confirmed pulmonary TB
- RR/MDR TB

Exclusion criteria:

- R vs bedaquiline, pretomanid, delamanid o linezolid
- Previous exposure to bedaquiline, pretomanid, delamanid o linezolid (≥ 4 weeks)
- Pregnancy or Breastfeeding
- Liver enzyme elevation > 3 times n.v.
- QTcFb > 450 ms
- Other known risk factors for QT prolongation/torsades de pointes
- History of cardiomyopathy, syncope, arrhythmia
- Last stage/end of life patient
- Severe adverse event (grade 4)
- Extrapulmonary TB (meningoencephalitis, cerebral tuberculoma, Pott disease, arthritis)



MDR TUBERCULOSIS – CONSIDERATIONS

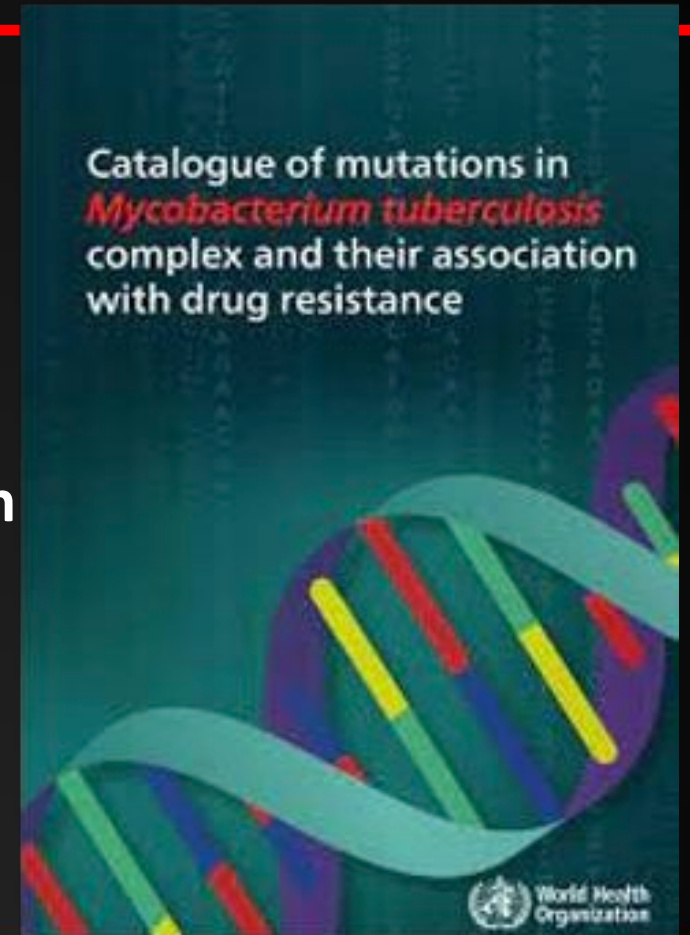
Implementation of new treatments for MDR/RR-TB not paired to diagnostics might lead to increased level of resistance worldwide.

Even before scaling-up BPalm implementation...

Worrisome levels of bedaquiline resistance (up to 47%) acquisition during bedaquiline-based regimens

Reports of pretomanid resistance

ACTION NEEDED: research on genotypic/phenotypic concordance of resistant for new drugs and DST availability



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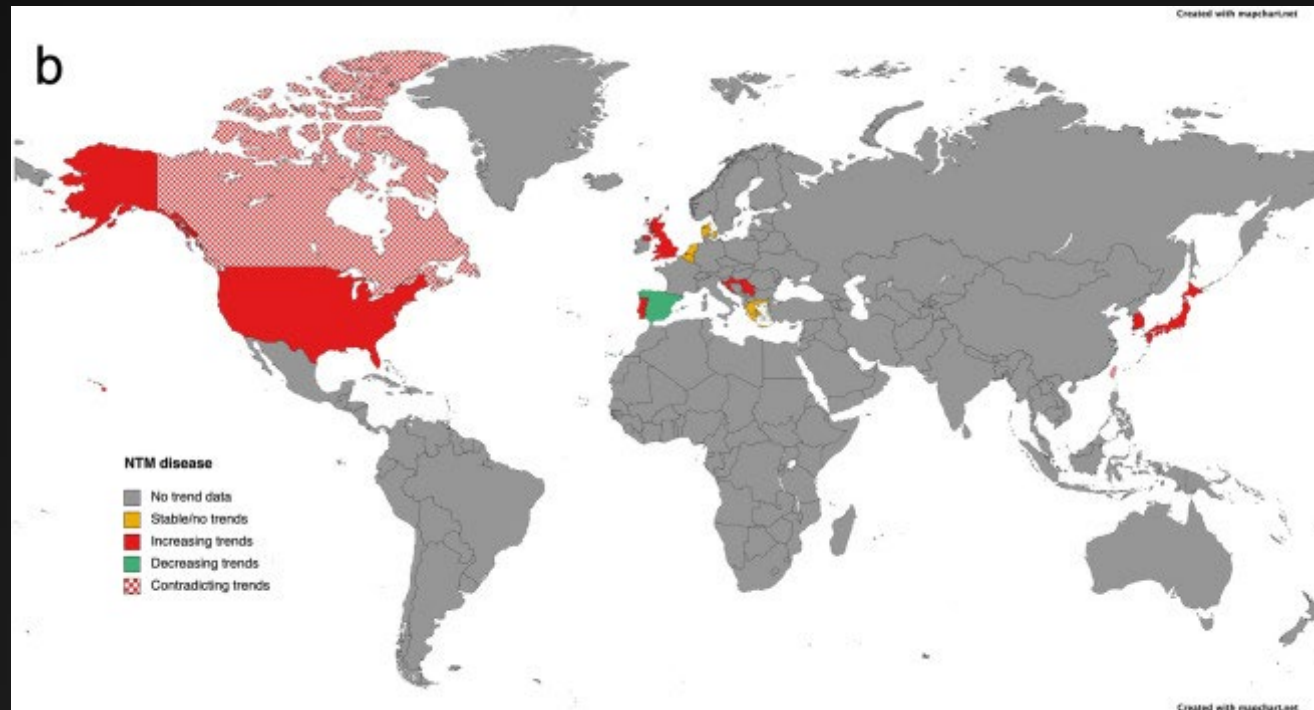
Saluzzo, Cirillo, J Clin Tuberc Other Mycobact Dis. 2023 Aug;

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NTM – DISEASE BURDEN

- High geographic diversity, NON-NOTIFIABLE disease, poorly understood epidemiology
- Increase in incidence worldwide ➡ more diagnostics? more immunosuppressants? longer life expectancy? increased awareness?



Dahl VN, *IJID* 2022

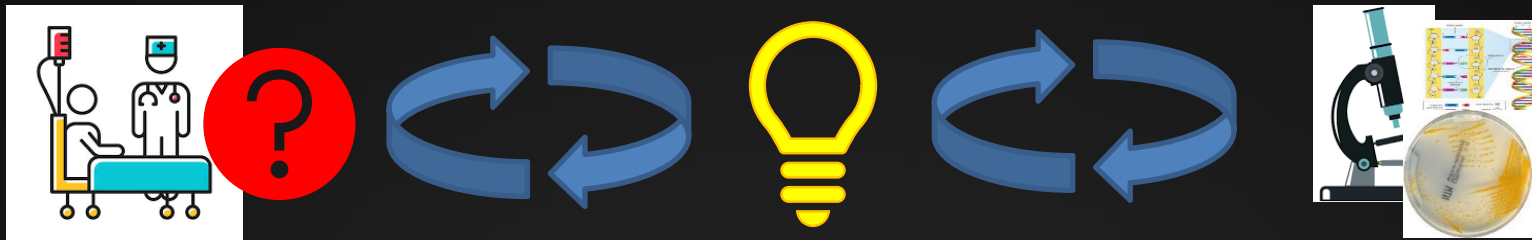


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NTM – DIAGNOSIS



**DIAGNOSING NTM DISEASE IS CHALLENGING AND REQUIRES:
HIGH CLINICAL SUSPICION TO TRIGGER DIAGNOSTIC TESTS AND AVOID DELAYS IN CARE
TRAINED LABORATORY FACILITIES
MULTIDISCIPLINARY APPROACH (ID/MICROBIOLOGY/SURGERY/PULMONOLOGY)**

Griffith DE, AJRCCM 2007

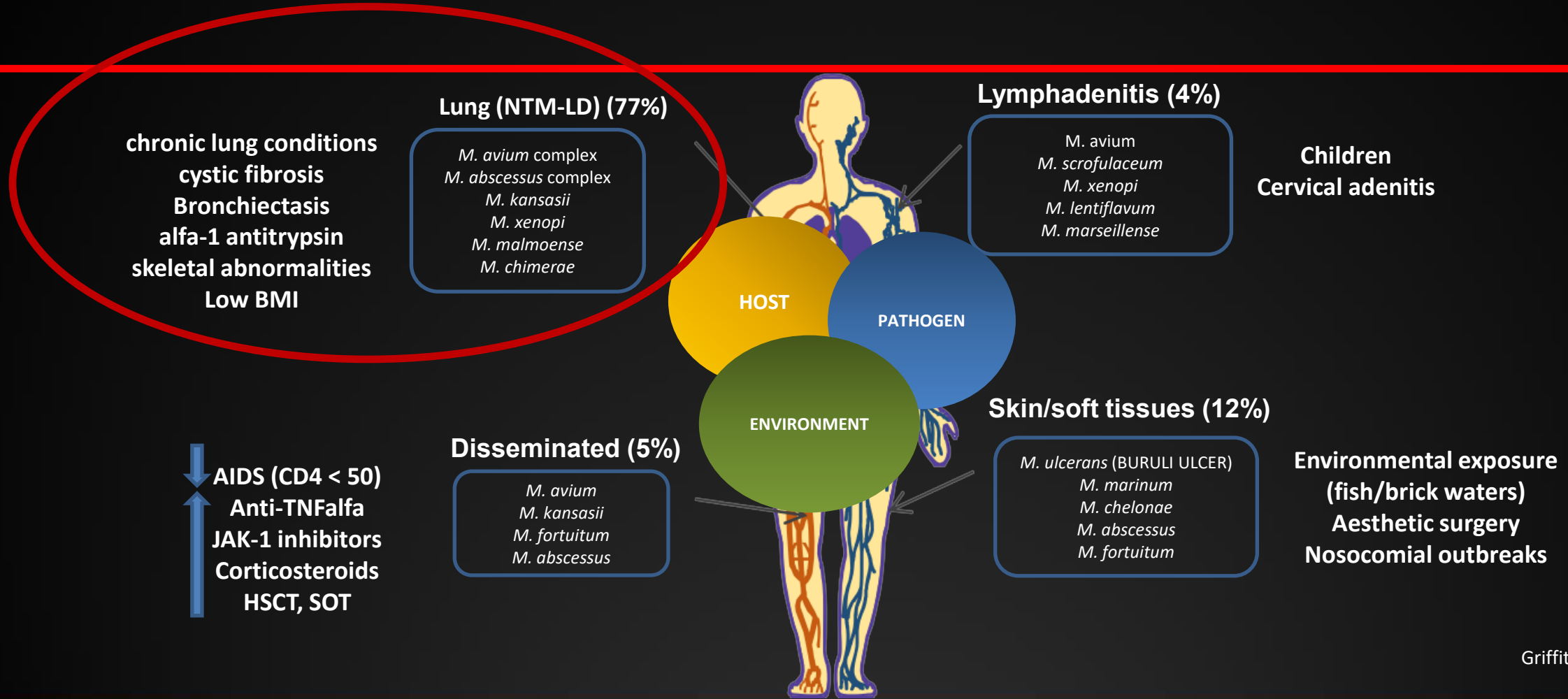


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NTM – DISEASE ENTITIES and RISK FACTORS



Griffith DE, AJRCCM 2007
Tortoli E, CMI 2009



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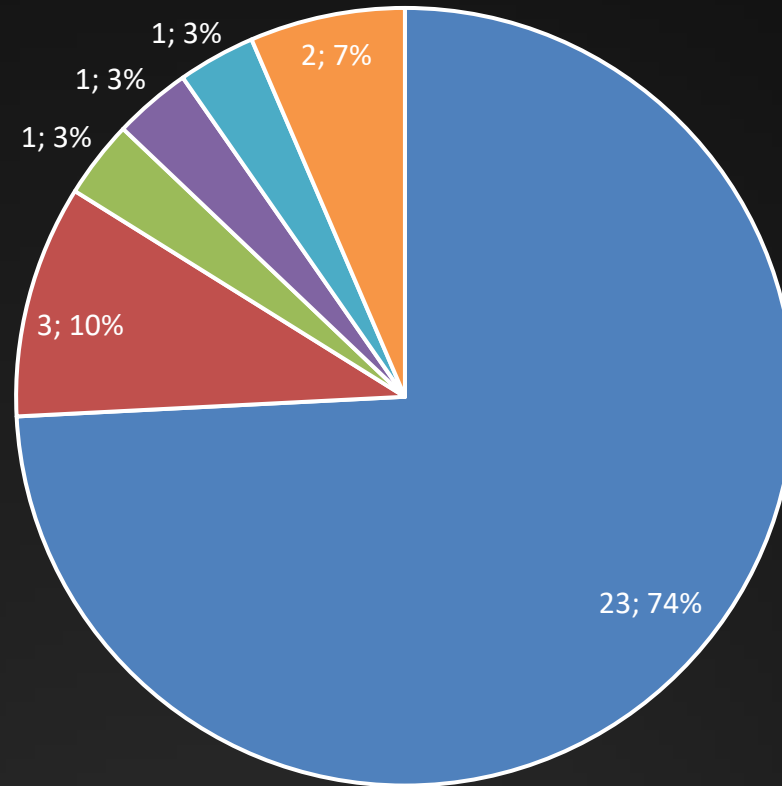
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NTM – REGISTRO IRENE, DATI HSM 2018 -2024

TOT=30

On treatment/treated = 22 (73%)



■ MAC (15 *M. avium*, 7 *M. intracellulare*) ■ *M. chimerae* ■ *M. szulgai* ■ *M. xenopi* ■ *M. chelonae* ■ Unknown



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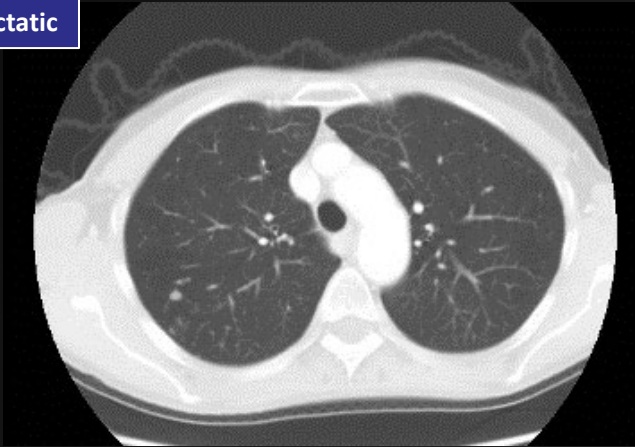
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NTM – *M. avium* complex (MAC) treatment considerations

Historically associated to disseminated disease in AIDS patients, now it is more frequently seen as a cause of NTM-lung disease and disseminated disease in immunocompromised patients other than PLHIV.

Nodular-bronchiectatic



Fibrocavitary



To treat or not to treat? CRITERIA:

CLINICAL + RADIOLOGICAL + MICROBIOLOGICAL (2 sputum/1 BALF culture)

Daley 2020, CID - Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline



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NTM – *M. avium* complex (MAC) treatment considerations

TREATMENT COMPOSITION:

Based on macrolide and amikacin susceptibility test:

AZITHROMYCIN + ETHAMBUTOL + RIFAMPICIN (daily/three weekly) + IV amikacin for severe disease

TREATMENT DURATION:

at least 12 month after culture conversion (optimal duration unknown, likely variable between patients)

FOLLOW-UP:

- **Symptomatic response** - e.g., Quality of Life-Bronchiectasis (QOL-B) questionnaire, health-related quality of life (HRQoL)
- **Drug-related adverse events** (visual acuity, auditory function, liver enzymes...)
- **Radiological monitoring** (HRCT, role of PET-FDG?)
- **Microbiology**: repeat culture every 1-2 months (BAL at 6th month if no sputum production)

Daley 2020, CID - Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline



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NTM – *M. avium* complex (MAC) treatment considerations

After 6 months

CULTURE CONVERSION?

Yes

Continue therapy
and monitoring

No (Refractory MAC disease)

THINK



Drug-levels?
Perform TDM

Resistance?
DST

Uncontrolled
underlying disease?
Repeat radiology,
physiotherapy,
nutrition, lung function tests?

Evaluate treatment modification:

+ Amikacin liposome inhalation suspension (ALIS)?
(recommended).

CONVERT TRIAL: 30% culture conversion vs 10% SoC
BUT >80% adverse events.

+ Clofazimine? Dose?

Patient-oriented decision making, quality of life

Daley CL, 2020, CID

Griffith DE, 2018 Am J Respir Crit Care Med



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Leprosy (Hansen's disease) – A forgettable disease?

Still > 200.000 cases/year. 216 in Europe since 2015 (mainly foreign-born)

HOW DO PATIENTS USUALLY PRESENT?

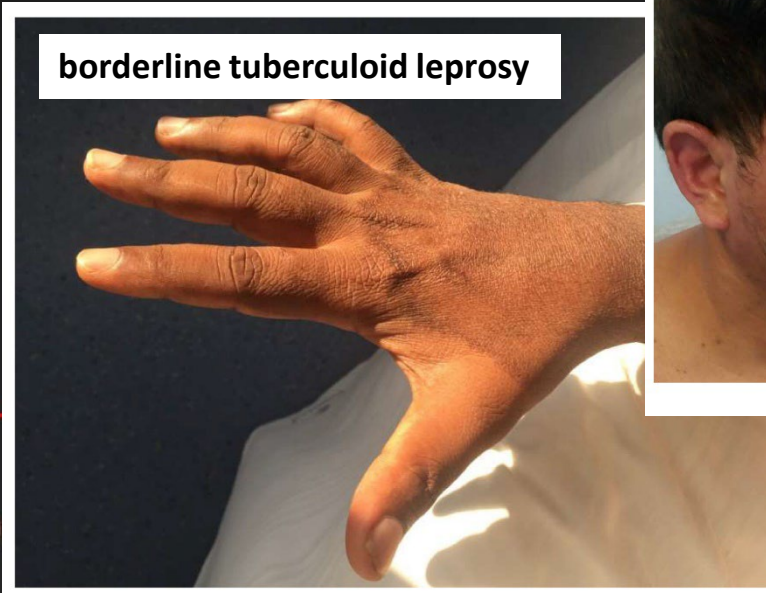
- Hypo pigmented and hypoaesthetic skin patch/es
- Red raised patch recent/sudden onset
- Unexplained burn or hand injury on foot
- New nerve function impairment, sensory/motor

Paucibacillary (PB)

1 to 5 skin lesions, negative skin smear



borderline tuberculoid leprosy



Multibacillary (MB)

> 5 lesion or nerve involvement or positive smear



Beltrame A, *Microorganisms* 2020

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Leprosy (Hansen's disease) – A forgettable disease?



CRITERIA through CARDINAL SIGNS (at least one)

- Definite loss of sensation in a hypopigmented or reddish skin patch
- Thickened or enlarged peripheral nerve with loss of sensation and/or weakness of muscles supplied by that nerve OR
- Presence of acid-fast bacilli in a slit-skin smear

MULTIPLE DIFFERENTIAL DIAGNOSES, BUT EPIDEMIOLOGICAL + SENSORY LOSS + PATCHES SHOULD RAISE SUSPICION

Multidrug Therapy (MDT): rifampicin 600 mg monthly, dapsone 100 mg daily, clofazimine 300 mg monthly, and 50 mg daily

6 months for paucibacillary leprosy and 12 months for multibacillary leprosy

BEWARE OF LEPROSY REACTIONS (inflammatory reaction under treatment)

WHO Expert Committee on Leprosy; 8° report 2012

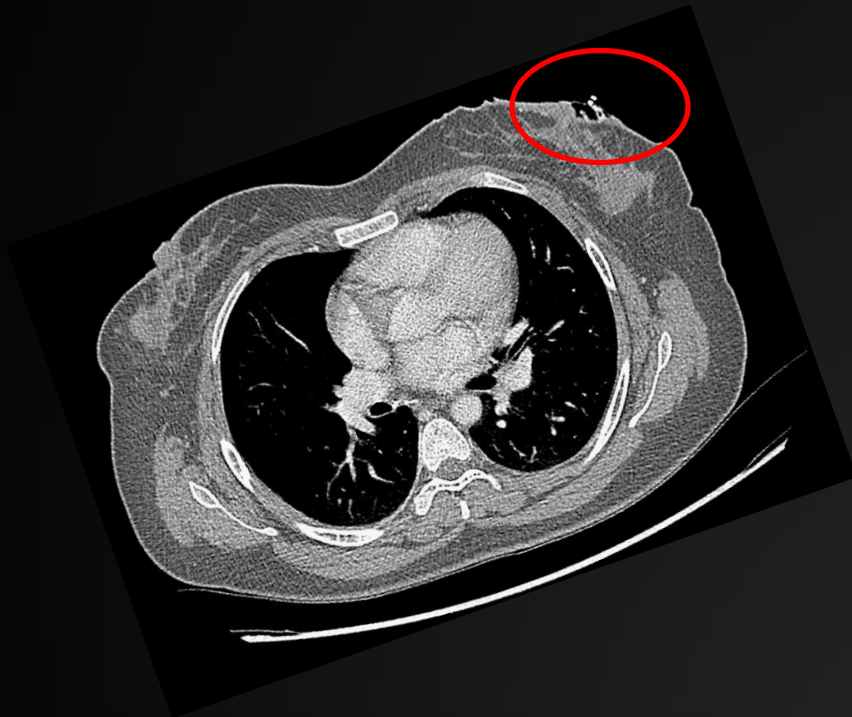


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NTM – skin and soft tissue disease



M. chelonae



M. ulcerans



M. marinum



NTM – skin and soft tissue disease



M. tuberculosis complex



Conclusions

- Know your epidemiology and practise active-case finding
- Be committed in diagnosis when there is a high clinical and epidemiological suspicion
- Avoid starting empirical anti-mycobacterial treatment
- Follow the guidelines
- Send samples to reference centers for second-line treatment DST and sequencing
- Work in team: microbiology, public health, pulmonology, dermatology, surgery
- Ensure access to treatment and close follow-up for underprivileged patients



Grazie per l'attenzione

They are everywhere

Antimicrobial resistance

Gaps in research

High morbidity and mortality

WHY MYCOBACTERIA?

Difficult to treat

Wide range of diseases

Difficult to diagnose

Diseases of poverty, neglected



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