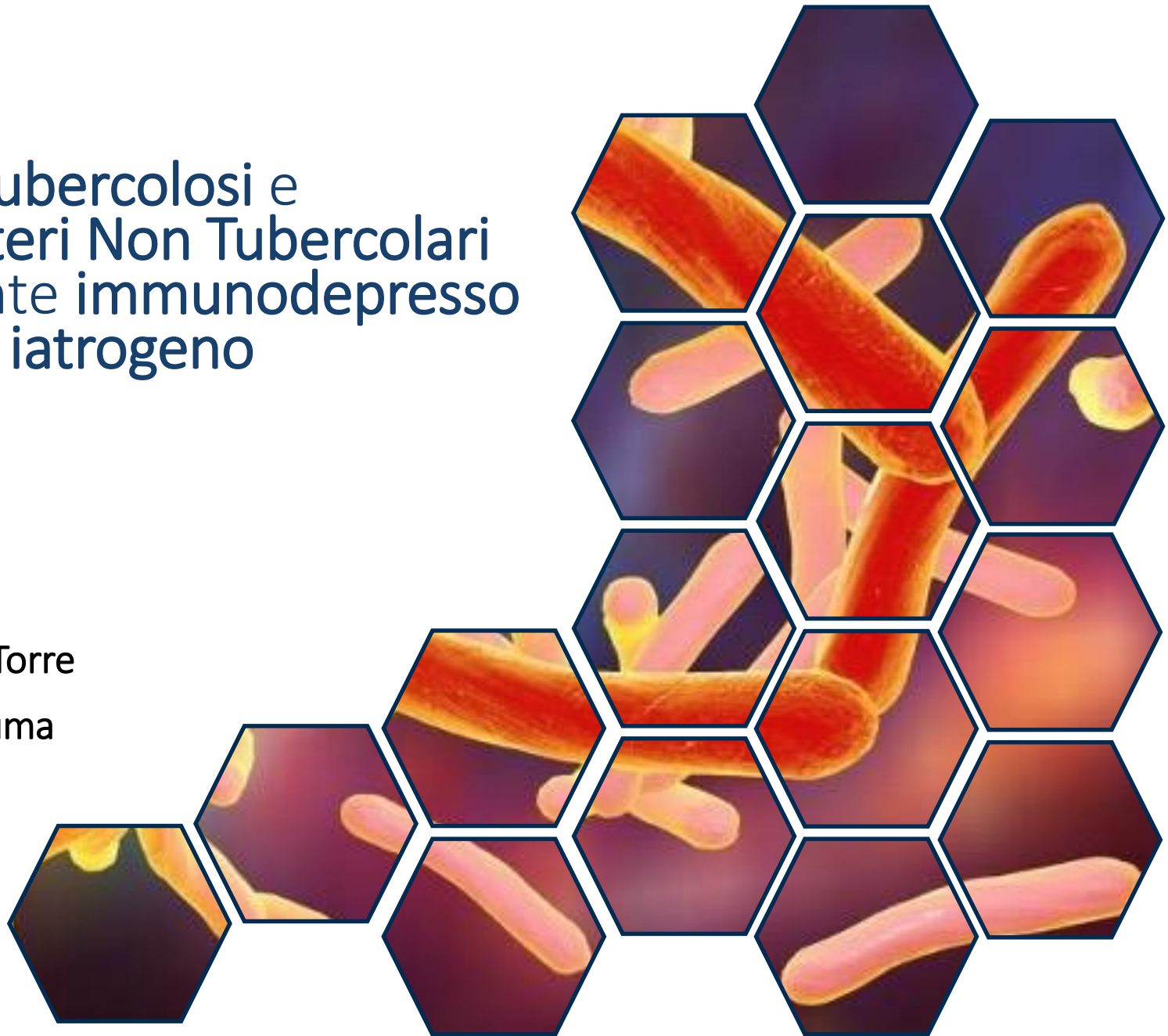


Tubercolosi e Micobatteri Non Tubercolari nel paziente immunodepresso iatrogeno

24 Marzo 2025

Dott. Alessandro Torre

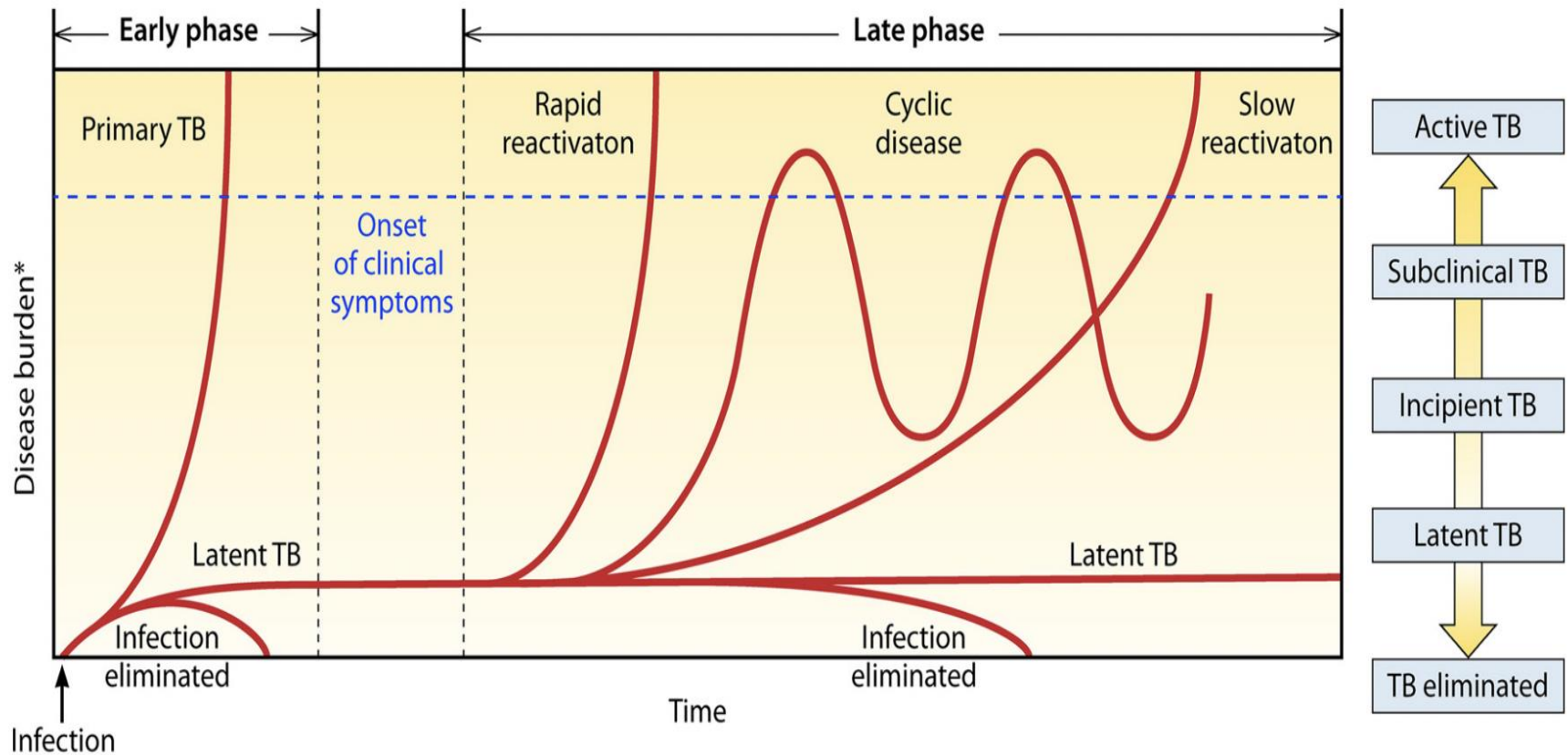
Dott. Marco Schiuma



Tubercolosi Epidemiologia

- 1 persona su 4 con infezione tubercolare → 2 Miliardi di persone!
- TB diagnosticate nel 2023: 10.8 Milioni
 - 30 Paesi ad alta incidenza: 87% dei casi
 - India, Indonesia, Cina, Filippine, Pakistan: 56% dei casi
 - In Italia: 2.700 casi (nel 2022)
- **Decessi causati da TB nel 2023 → 1.25 Milioni**
 - Prima agente patogeno per mortalità
 - In Italia: 300 decessi (nel 2022)

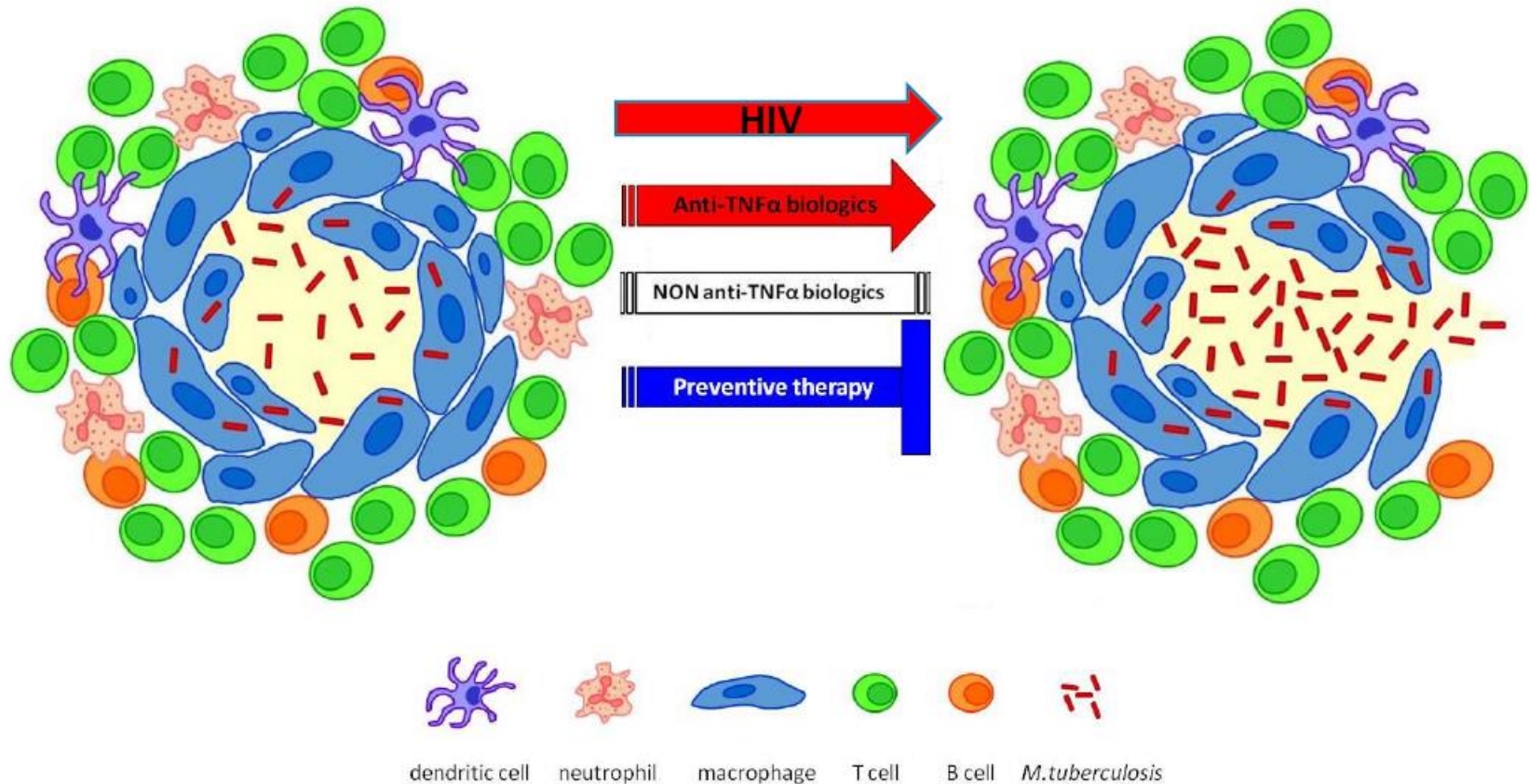
Fisiopatologia



*Rising TB burden implies an increase in abundance of TB and pathogen biomarkers, compartment-specific changes in immunological responses, and a decrease in the probability of disease resolution in the absence of treatment.

Fisiopatologia

Integrità del granuloma è cruciale per controllare la TB



Risk of Developing Active TB

A) HIGH RISK (ANY AGE)

Risk for reactivation ≥ 6 times LRR (Low Risk Reactor)



1. HIV infection

risk x 50 – 170, annual risk 13% (CD4+ < 200), 7% (CD4+ 200-350), 3% (CD4+ > 350)

2. IMMUNOCOMPROMISED

transplant risk x 20 - 74, TNF-alfa inhibitor risk x 2-9, chemotherapy

3. CANCER

lymphoma, leukemia, head-neck cancer risk x 16

4. CHRONIC RENAL FAILURE

end stage, requiring dialysis, risk x 30

5. CXR abnormalities

apical fibronodular changes typical of “inactive” TB (not granulomas), risk x 6 - 19

6. SILICOSIS

risk x 30

Risk of Developing Active TB

B) MODERATE RISK (age < 65)

Risk for reactivation 3-6 times LRR (Low Risk Reactor)

1. GLUCOCORTICOIDS

prednisone > 15 mg/day for ≥ 1 month, risk x 5

2. DIABETES

risk x 2-3

3. INFECTED < 4 years old

risk x 2-5



Farmaci Biologici

<i>Farmaci</i>	<i>Rischio TB/NTM</i>	<i>Meccanismo Azione</i>	<i>Screening TBI</i>
Anti-TNF Adalimumab, Certolizumab Etanercept, Infliximab, Golimumab	Aumento 2-9 volte del rischio di TB; Aumento rischio di NTM	Riducono IL-1, IL-6; Riducono migrazione tissutale di cellule infiammatorie; Riducono capacità di formazione e mantenimento del granuloma	Raccomandato
Anti-IL-6 Tocilizumab, Siltuximab, Sarilumab	Descritti casi di TB, NTM	Blocco IL-6	Raccomandato
Anti-IL-1 Anakinra, Canakinumab, Gevokizumab, Rilonacept	Possibile incremento	Riduzione NF-kB, reclutamento neutrofili	Considerare
Anti-IL-12/23 Ustekinumab	Descritti casi di TB	Blocco IL-12/23	Considerare

Farmaci Biologici

<i>Farmaci</i>	<i>Rischio TB/NTM</i>	<i>Meccanismo Azione</i>	<i>Screening TBI</i>
Anti-IL-17 Secukinumab, Ixekizumab Brodalumab	Possibile incremento	Blocco del rilascio di citochine e chemochine proinfiammatorie	Considerare
Inibitori TK, BCR-ABL Imatinib, Dasatinib	Descritti casi di TB	Inibizione TK, Neutropenia, ridotta attivazione CD4+ e CD8+, riduzione della risposta B cellulare	Nessuna raccomandazione
Inibitori JAK Ruxolitinib, Tofacitinib, Baricitinib	Descritti casi di TB	Ridotta produzione di citochine, inibizione differenziazione in Th1 e Th17	Raccomandato
Inibitori mTOR Sirolimus, Everolimus	Descritti casi di TB	Compromissione immunità innata; Ridotta migrazione neutrofili; Ridotta produzione citochine proinfiammatorie;	Raccomandato

Farmaci Biologici

<i>Farmaci</i>	<i>Rischio TB/NTM</i>	<i>Meccanismo Azione</i>	<i>Screening TBI</i>
Anti-CD52 Alemtuzumab	Descritti casi di TB	Deplezione cellule CD52+ (linfociti, monociti, macrofagi, cellule epiteliali), Deplezione linfociti B e T	Raccomandato
Anti-CTLA4 Ipilimumab, Tremelimumab	Aumento del rischio	Up-regolazione dei linfociti T stimolati dalle cellule dendritiche	Raccomandato
Anti-PD-1/PD-L1 Nivolumab, Pembrolizumab Atezolizumab	Descritti fenomeni di IRIS TB	Up-regolazione del sistema immunitario, promuovono l'attività effettrice dei linfociti T	Raccomandato

Risk of Developing Active TB

tstin3d.com/calc.html

1. Input Your Information

What is your age

40

What is the size of your TST (Skin Test)

5-9mm or Not Done

What is your IGRA result (Blood Test)

Not Done

Please Check All That Applies Below:

- ☒ Habits
- ☒ TB Exposure
- ☒ Cancer
- ☒ Immune-Compromised
- ☒ Immunosuppressive Treatment
- ☒ TB-related Chest X-Ray findings

Uncheck All Selection

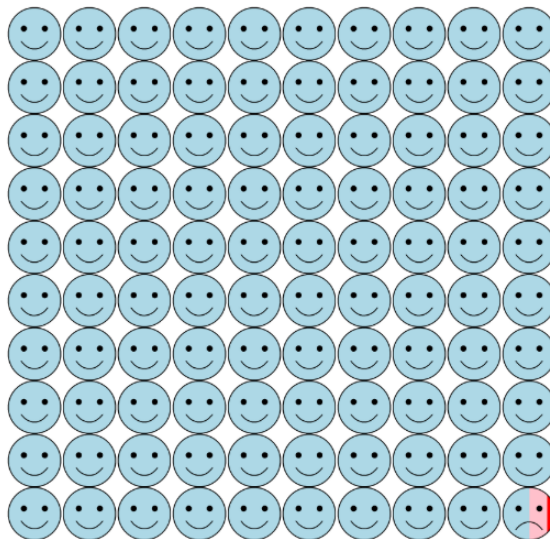
2. Your TB Risk (Over the Next 20 Years)

Healthcare Provider

Patient

FAQ

What is the risk of TB disease in the next 20 years without treatment? Out of 100 persons with the risk factors selected:



99.5% Will not develop TB disease with or without treatment



0.5% will develop TB disease without treatment



0.1% will develop TB disease and TB-related long-term disability or death without treatment

3. Input Preventive Treatment

Select one of the following treatment options:

- ☒ No Treatment
- ☐ 4 months of daily rifampin (4R)
- ☐ 9 months of daily isoniazid (9H)
- ☐ 3 months of once-weekly isoniazid plus rifapentine (3HP)
- ☐ 3 months of daily isoniazid plus rifampin (3HR)

For drug interactions, see [Medscape Drug Interaction Checker](#)

4. Summary of your TB Risk

Without Treatment

- Your risk of TB disease without treatment in the next 20 years: 0.5%
- Your risk of disability and death from TB disease without treatment in the next 20 years: 0.1%

Download Patient Handout

The Online TST/IGRA Interpreter

☒ Habits

☐ Cigarette Smoker (≥ 1 Pack Per Day)

☒ TB Exposure

☐ Casual Contact

☐ Close Contact

☐ Recent Immigration (within the past 5 years)

☐ Occupational Risk (Healthcare Worker)

☒ Cancer

☐ Head & Neck Carcinoma

☐ Hodgkin's Lymphoma

☐ Non Hodgkin's Lymphoma

☐ Lung Cancer

☒ Immune-Compromised

☐ HIV on effective ART

☐ Chronic Kidney Disease on dialysis

☐ Diabetes Any Type

☐ Silicosis

☐ Liver Transplant

☐ Kidney Transplant

☒ Immunosuppressive Treatment

☐ Steroids, at least 10mg of prednisone daily (or equivalent)

☐ TNF-alpha Inhibitors

☒ TB-related Chest X-Ray findings

☐ Fibronodular Disease

☐ Granuloma

The Online TST/IGRA Interpreter

1. Input Your Information

What is your age

45

What is the size of your TST (Skin Test)

5-9mm or Not Done

What is your IGRA result (Blood Test)

Positive

Please Check All That Applies Below:

☒ Habits

☒ TB Exposure

☒ Cancer

☒ Immune-Compromised

☒ Immunosuppressive Treatment

☐ Steroids, at least 10mg of prednisone daily (or equivalent)

☒ TNF-alpha Inhibitors

☒ TB-related Chest X-Ray findings

Uncheck All Selection

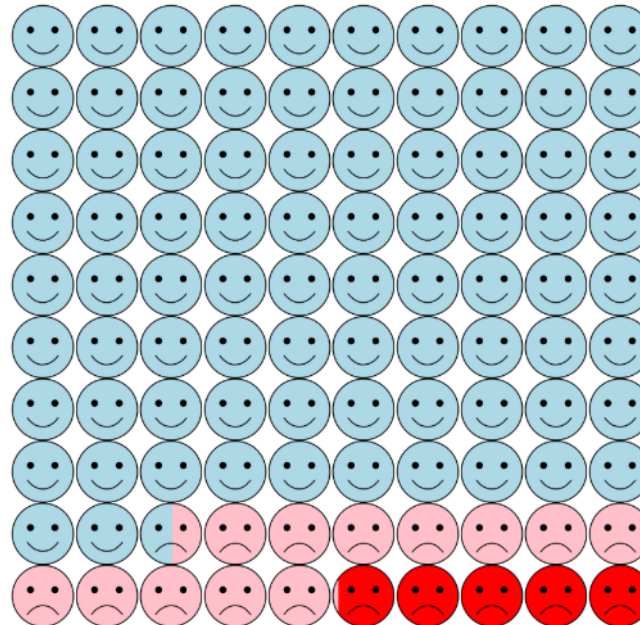
2. Your TB Risk (Over the Next 20 Years)

Healthcare Provider

Patient

FAQ

What is the risk of TB disease in the next 20 years without treatment? Out of 100 persons with the risk factors selected:



82.5% Will not develop TB disease with or without treatment



17.5% will develop TB disease without treatment

The Online TST/IGRA Interpreter

1. Input Your Information

What is your age

75

What is the size of your TST (Skin Test)

5-9mm or Not Done

What is your IGRA result (Blood Test)

Positive

Please Check All That Applies Below:

☒ Habits

☒ TB Exposure

☒ Cancer

☒ Immune-Compromised

☒ Immunosuppressive Treatment

☒ Steroids, at least 10mg of prednisone daily (or equivalent)

☐ TNF-alpha Inhibitors

☒ TB-related Chest X-Ray findings

Uncheck All Selection

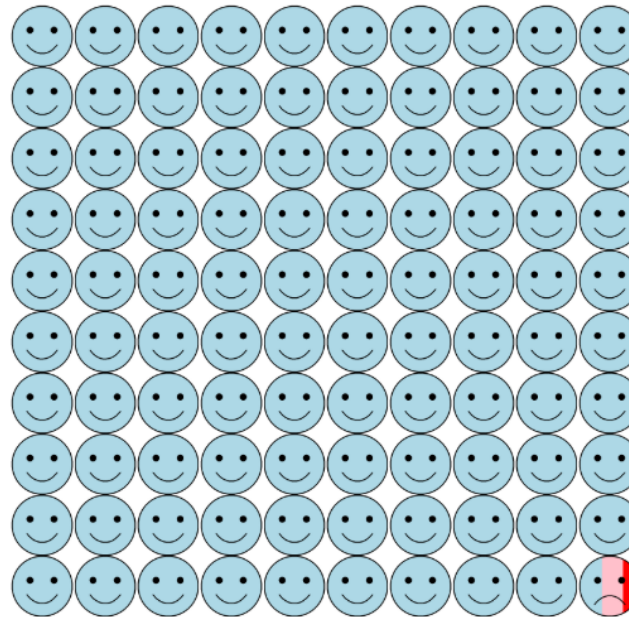
2. Your TB Risk (Over the Next 20 Years)

Healthcare Provider

Patient

FAQ

What is the risk of TB disease in the next 20 years without treatment? Out of 100 persons with the risk factors selected:



99.4% Will not develop TB disease with or without treatment



0.6% will develop TB disease without treatment

The Online TST/IGRA Interpreter

1. Input Your Information

What is your age

25

What is the size of your TST (Skin Test)

5-9mm or Not Done

What is your IGRA result (Blood Test)

Positive

Please Check All That Applies Below:

☒ Habits

☒ TB Exposure

☒ Cancer

☒ Immune-Compromised

☐ HIV on effective ART

☐ Chronic Kidney Disease on dialysis

☐ Diabetes Any Type

☐ Silicosis

☒ Liver Transplant

☐ Kidney Transplant

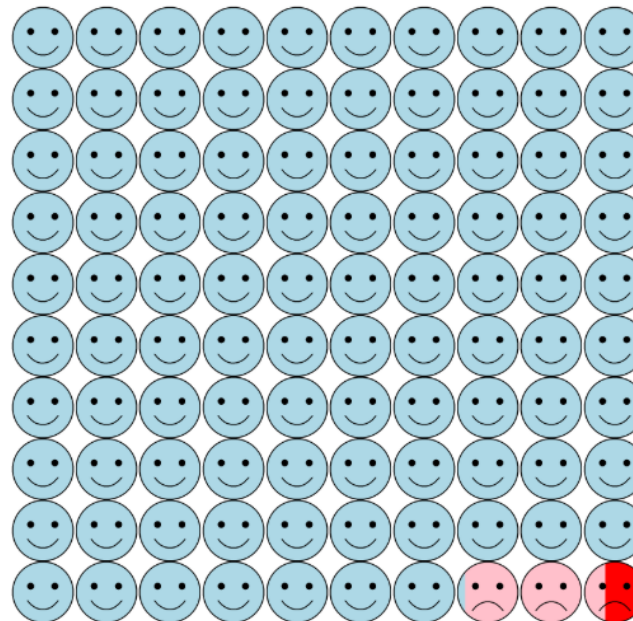
2. Your TB Risk (Over the Next 20 Years)

Healthcare Provider

Patient

FAQ

What is the risk of TB disease in the next 20 years without treatment? Out of 100 persons with the risk factors selected:



97.1% Will not develop TB disease with or without treatment



2.9% will develop TB disease without treatment

Caso Clinico 1

- MP, uomo, 39 anni, italiano
- **Artrite e spondilite psoriasica** (2013); trattato prima con steroide e metotrexate, successivamente con adalimumab (fino al 04/2021).
- **Infezione tubercolare latente**: Quantiferon-TB negativo (2017), poi positivo (2019); effettuato trattamento preventivo con rifampicina per 4 mesi (concluso 10/2019).

Caso Clinico 1

- Dal 12/2020 seguito presso **Gastroenterologia** per quadro di **ileite terminale** associato a **calo ponderale** di 12 Kg.
- Dopo esecuzione di **colonscopia**, **TC** e **RM addome**, si pone diagnosi di **sospetta malattia di Crohn** e si imposta terapia con **infliximab** (04/2021).
- Dal 03/05/2021 comparsa di **febbre** ed **addominalgia**, per cui accedeva presso PS dove esegue TC addome con mdc

Caso Clínico 1



Caso Clínico 1



Caso Clinico 1

- **TC addome con mdc (21/05):** rispetto al precedente controllo, **progressione della malattia infiammatoria** a livello dell'ultima ansa ileale, dove la parete appare maggiormente edematosa e iperemica. Si evidenzia interessamento analogo di un'ulteriore porzione d'ansa in sede centro-addominale, con diffuso edema parietale delle altre anse intestinali. Incremento dimensionale delle **linfadenopatie** poste lungo il mesentere in adiacenza dell'ultima ansa ileale, la maggiore di **35 mm vs 25 mm**. Diffusa **imbibizione del mesentere** in corrispondenza della anse interessate da flogosi acuta.

Caso Clinico 1

- Esami microbiologici per la **ricerca di micobatteri** su **feci**:
 - Microscopico negativo
 - PCR per *M. tuberculosis*-complex positiva (resistenza genotipica alla rifampicina)
 - Colturale in corso (successivamente inquinato)
- **Linfoadenectomia addominale**:
 - Microscopico negativo
 - PCR per *M. tuberculosis*-complex positiva (resistenza genotipica alla rifampicina)
 - Colturale in corso (successivamente positivo per *M.tuberculosis*-complex, confermato resistenza R, ceppo **XDR** con resistenza a RHZE, Fq, Bdq, Cfz)

Caso Clinico 2

- QL, uomo, 53 anni, italiano
- **Sacroilete HLA B27 negativa** (2009); trattato prima con steroide, sulfasalizna, adalimumab, successivamente con certolizumab (dal 05/2022).
- Quantiferon-TB negativo (04/2022)

Caso Clinico 2

- 12/2022 comparsa di febbre (TA max 38°C), sudorazioni notturne, calo ponderale 4 Kg in 2 mesi
- **RX torace:** negativa
- **Ecografia addome:** milza con numerose lesioni a bersaglio
- **TC addome con mdc**
- **TC torace con mdc**

Caso Clínico 2



Caso Clínico 2



Caso Clinico 2

- Esami microbiologici per la **ricerca di micobatteri** su **BAL**:
 - Microscopico negativo
 - PCR per *M. tuberculosis*-complex positiva
 - Colturale positivo per *M. tuberculosis*-complex

Tuberculosis in Transplant Recipients

Epidemiology

- Most commonly **reactivation** of TB infection in the **recipient**
- Less commonly **new infection after transplantation**
- May also arise from **unrecognized TB infection** in the **allograft**
- *Timing*: occurs **earlier** among **lung transplant** recipients than among renal transplant recipients; **donor-derived** TB disease typically occurs **earlier** than the reactivation of TB infection that originated in the recipient

Tuberculosis in Transplant Recipients

Clinical features

- **Disseminated / extrapulmonary** sites 30-50%
- Most common extrapulmonary sites: **pleura, lymph nodes, bone**
- May have **atypical presentation**: pyomyositis, cutaneous ulcers or abscess, tenosynovitis

Non Tuberculous Mycobacteria

Main Clinical Syndromes

A) **LYMPHADENITIS** (children, generally cervical)

- 1) *Mycobacterium avium-complex* (MAC)
- 2) *Mycobacterium scrofulaceum*
- 3) *Mycobacterium haemophilum*

B) **SKIN / SOFT TISSUE** (direct inoculation)

- 1) *Mycobacterium marinum*
- 2) *Mycobacterium ulcerans*
- 3) RGM (*M. abscessus*, *M. fortuitum*, *M. chelonae*)

C) **DISSEMINATED DISEASE** (immunocompromised)

- 1) *Mycobacterium avium-complex* (MAC)
- 2) RGM (*M. abscessus*, *M. fortuitum*, *M. chelonae*)

D) **LUNG DISEASE**

SLOWLY GROWING (SGM)

- 1) *M. avium-complex* (MAC)
 - a) *M. avium*
 - b) *M. intracellulare*
 - c) *M. chimaera*
- 2) *M. kansasii*
- 3) *M. xenopi*

RAPIDLY GROWING (RGM)

- 1) *M. abscessus* (MAB)
 - a) subsp *abscessus*
 - b) subsp *massiliense*
 - c) subsp *bolletii*

Non Tuberculous Mycobacteria in Transplant Recipients

Epidemiology

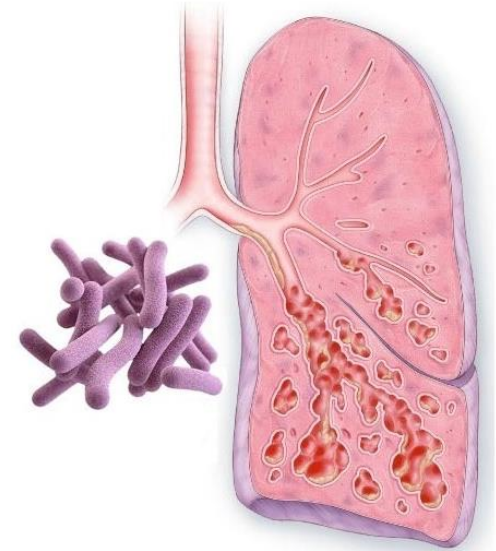
- Most species found in **soil** and **water**
- The majority of infections arise from **environmental exposure**
- **Human-to-human** spread of *Mycobacterium abscessus* among patients in cystic fibrosis centers and on a population level has been reported
- Solid organ transplant (SOT) recipients have an increased risk for infection with NTM due to **depressed cell-mediated immunity**

Non Tuberculous Mycobacteria in Transplant Recipients

Risk Factors

LUNG TRANSPLANT RECIPIENTS

- NTM disease or colonization pre-transplant
- Cystic fibrosis (CF)
- Use of anti-thymocyte globulin for induction immunosuppression



Non Tuberculous Mycobacteria in Transplant Recipients

Risk Factors

ALL ORGAN TRANSPLANT RECIPIENTS

- Older age
- Recent Hospital Admission (< 90 days)
- Receipt of Antifungals
- Receipt of lymphocyte depleting antibodies



Non Tuberculous Mycobacteria in Transplant Recipients

Clinical features

- Median **onset** of NTM infection: ≥ 1 **year** after transplantation
- **Cutaneous, musculoskeletal, disseminated** infections most common presentations especially in non-lung solid organ transplant recipients
- **Pleuropulmonary** disease most common in lung transplant recipients

Take Home Messages

- **Disseminated / extrapulmonary** more frequent
- **Atypical presentation** (pyomyositis, cutaneous ulcers/abscess, tenosynovitis)
- **Diagnosis more challenging** (increased likelihood of negative TST/IGRA, sputum negative)