🦠 "Mycobacteria"

📌 General Features

- Aerobic, acid-fast bacilli (AFB) → Slender, straight or slightly curved rods 🔬
- Not Gram-positive or Gram-negative → Poorly stained by Gram stain due to lipid-rich cell wall

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🔹 Acid-Fast Property (Very High-Yield)

- Due to very high lipid content (~60%) in cell wall
- Major lipid component: Mycolic acids
  - Long-chain fatty acids (C78–C90)
- Retain carbol fuchsin dye even after washing with acid-alcohol (ethanol + HCl)

📌 Exam Pearl:

👉 Acid-fastness = mycolic acids in cell wall

🔹 Unique Characteristics

- Almost all acid-fast bacteria = Mycobacteria
- Important exception → *Nocardia asteroides* (weakly acid-fast)

🧬 Medically Important Mycobacteria

📊 Table: Important Mycobacteria

Species	Growth Rate	Preferred Temp (°C)	Source / Transmission
M. tuberculosis	Slow (weeks)	37	Respiratory droplets
M. bovis	Slow (weeks)	37	Unpasteurized milk 🐄
M. leprae	❌ No growth in culture	32	Prolonged close contact
M. kansasii	Slow (weeks)	37	Soil & water

M. marinum	Slow (weeks)	32	Water (aquatic infections)
M. avium-intracellulare (MAC)	Slow (weeks)	37	Soil & water
M. fortuitum-chelonae	Rapid (days)	37	Soil & water

📌 Exam Pearl:

👉 *M. leprae* cannot be cultured in vitro

📊 Clinical Correlation – Key Mycobacteria

Organism	Main Site	Skin Test	Multidrug Therapy	Vaccine
M. tuberculosis	Lungs	Yes (PPD/TST)	Yes	Yes (BCG)
MAC	Lungs	No	Yes	No
M. leprae	Skin, nerves	No	Yes	No

🧠 "Mycobacterium tuberculosis"

🌍 Global Burden (Very Important)

- Most lethal single microbial agent worldwide
- ~1/3 of world population infected
- Annual burden:
  - ~9 million new cases
  - ~1.7 million deaths
  - ~500,000 MDR-TB cases

📌 Exam Pearl: TB > HIV > Malaria in mortality (single organism)

🔬 Important Properties

🔹 Growth Characteristics

- Very slow growth
  - Doubling time: ~18 hours
  - (Most bacteria ≈ 1 hour)

- Cultures declared negative only after 6–8 weeks
- Culture medium:
    - Löwenstein–Jensen medium
        - Egg-based
        - Contains malachite green → inhibits contaminants

🔹 Oxygen Preference

- Obligate aerobe
- Prefers high oxygen tension tissues:
    - Upper lobes of lungs 🫁
    - Kidney

📌 Exam Pearl: Reactivation TB → lung apices

🔹 Cell Wall Composition (Highly Tested)

- Mycolic acids → Acid-fastness, resistance to drying
- Cord factor (trehalose dimycolate)

    - Major virulence factor
    - Causes serpentine cord formation
- Phthiocerol dimycocerosate
    - Essential for lung pathogenesis
- Proteins + waxes
    - Induce delayed-type hypersensitivity
    - Basis of PPD test

🔹 Resistance Features

- Resistant to acids & alkalis → NaOH used to digest sputum (kills other flora, spares TB)
- Survives in dried sputum → Facilitates airborne transmission

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🔹 Drug Resistance (Exam Favorite)

- INH resistance due to mutation in:
    - Mycolic acid synthesis gene OR

    - Catalase-peroxidase enzyme (activates INH)
- MDR-TB

  → Resistance to isoniazid + rifampin
- Resistance is due to:
    - Chromosomal mutations
    - ❌ No plasmids

🔄 Flowchart: Key Features of *M. tuberculosis*

Respiratory droplet inhalation → Entry into alveoli (upper lobes favored – high O_2) → Extremely slow growth (18-hour doubling time) → Weeks required for culture positivity → Virulence factors act:

- Cord factor → serpentine growth, macrophage inhibition
- Mycolic acids → acid-fastness, survival
- Phthiocerol dimycocerosate → lung damage

→ Induces delayed hypersensitivity → Positive PPD test

🔹 Transmission & Epidemiology

Transmission

- Person-to-person via respiratory aerosols
- Source:
  - Lung cavity eroding into bronchus
- Portal of entry: Respiratory tract
- Initial site: Lungs

Fate in Tissue

- Phagocytosed by macrophages
- Outcomes:
  - Most bacilli destroyed ✅
  - Some survive ❌ → replicate or disseminate

Reservoir

- Humans = primary reservoir
- Animals may be infected but are not main source

Smear Status

- Smear-positive cases → most contagious
- Smear-negative cases → ~20% transmission

M. bovis

- Source: Unpasteurized milk 🥛
- Causes GI tuberculosis

📊 Risk Factors for TB

Risk Factors for Infection	Risk Factors for Reactivation
Foreign born (high-TB area) 🌍	HIV/AIDS 🦠
Close contact with TB patient	TNF-α inhibitors
Homelessness / poor housing	Transplant drugs
Incarceration	Corticosteroids
IV drug use 💉	Diabetes

Health-care workers 🩺	Smoking 🚬

🔹 Pathogenesis

🔸 Primary Tuberculosis

Inhaled bacilli → Reach alveoli → Phagocytosed by macrophages → Survive inside phagosomes → Exudative lesion in lower lung → Ghon focus

Outcomes:

- 90% → Latent TB
- 10% → Active disease
- Latent TB → 10% lifetime reactivation risk

🔸 Secondary (Reactivation) TB

- Occurs in upper lobes
- Causes:
  - Cavitary lung lesions
  - Dissemination to:

- CNS → meningitis
- Spine → Pott's disease
- Kidney, bone

- Bacterial Virulence Factors
  - No exotoxin or endotoxin
  - Important proteins:
    - Tuberculosis necrotizing toxin (TNT) → NAD cleavage → macrophage death
    - ESAT-6 → Inhibits IFN-γ response
    - Exported repetitive protein → Prevents phagosome-lysosome fusion

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- Lesions

1. Exudative Lesions
   - Acute inflammatory response
   - Seen early at infection site

2. Granulomatous Lesions

- Central Langhans' giant cells
- Surrounding epithelioid cells + fibrosis
- Caseous necrosis
- Heal by fibrosis & calcification

🔸 Ghon Complex

- Ghon focus (lung lesion)
- Draining hilar lymph nodes

📌 Primary TB → lower lobes
📌 Reactivation TB → apices

🔸 Spread of Tuberculosis

1. Bronchogenic Spread

- Tubercle erodes into bronchus
- Bacilli spread within lungs

- Swallowed → GI TB
- Increases transmission

2. Hematogenous Spread

- Early → Miliary TB
- Late → Reactivation in organs

🔄 Flowchart: Overall Pathogenesis of TB

Primary infection (non-immune host, child) → Primary TB (Ghon focus – lower lobes) → Heals by fibrosis → Dormant bacilli → Latent TB → PPD positive

– OR –

→ progressive lung disease (HIV, malnutrition) → Death

– OR –

→ lymphatic/hematogenous spread → Miliary TB → Death

– OR –

→ latent TB reactivates later → Secondary TB (upper lobe cavities) → May disseminate:

- CNS → Tuberculoma / meningitis
- Spine → Pott's disease
- Lymph nodes → Scrofula
- Kidney, GI tract, adrenals

🔹 Immunity & Hypersensitivity

Protective Immunity

- Cell-mediated immunity (Th1 CD4+ cells)
- Activated macrophages kill bacilli
- Antibodies → no protective role

Key Cytokine

- IFN-γ → Activates macrophages

- Deficiency (AIDS, IFN-γ receptor defect) → Severe disseminated TB

Tuberculin Skin Test (Mantoux / PPD)

- Type IV delayed hypersensitivity
- Read at 48–72 hours
- Measure induration, not erythema

Cut-off Values:

- ≥ 15 mm → No risk factors
- ≥ 10 mm → Moderate risk
- ≥ 5 mm → High risk (HIV, immunosuppressed)

False Results

- False positive → Prior BCG
- False negative → AIDS, measles, early infection
- Booster effect → Repeat test amplifies response

🔹 Genetic Resistance

- Nramp gene
  - Encodes phagosomal protein
  - Enhances intracellular killing
- Mutation → ↑ TB susceptibility

🔹 Clinical Findings

🌡️ General (Constitutional) Symptoms

Seen in both pulmonary and extrapulmonary TB due to chronic inflammation:

- Fever
- Fatigue 😓
- Night sweats 🌙
- Weight loss ⚖️⬇️

📌 Exam Pearl: These are nonspecific but should raise suspicion in endemic areas.

🫁 Pulmonary Tuberculosis

- Symptoms:
  - Chronic cough
  - Hemoptysis (blood in sputum)
- Chest X-ray findings:
  - Upper lobe infiltrates
  - ± Cavitary lesions
    → Suggests reactivation (secondary) TB

📌 Upper lobes affected due to high oxygen tension.

🌍 Extrapulmonary Tuberculosis

🔹 Lymphadenitis (Scrofula)

- Cervical lymph nodes
- Swollen, non-tender

- Most common extrapulmonary TB
- More extensive in HIV patients

🔹 Skin

- Erythema nodosum
  - Tender nodules on tibia/ulna
  - Indicates good cell-mediated immunity

🔹 Miliary TB

- Hematogenous dissemination
- Numerous millet seed-like lesions throughout body
- Seen in:
  - Infants
  - Immunocompromised
- High mortality ⚠️

🔹 Central Nervous System

- Tuberculous meningitis
- Tuberculoma (space-occupying lesion)

- Skeletal System
  - Vertebral osteomyelitis → Pott's disease
  - Back pain, deformity, neurological deficits

- Gastrointestinal TB
  - Symptoms:
    - Abdominal pain
    - Diarrhea
    - Fever
    - Weight loss
  - Most common site: Ileocecal region
  - Complications:
    - Intestinal obstruction
    - Hemorrhage

Etiology:

- *M. tuberculosis* → swallowed infected sputum
- *M. bovis* → unpasteurized milk 🥛
- Oropharyngeal TB:
    - Painless ulcer
    - Cervical adenopathy

🔹 Renal TB

- Dysuria
- Hematuria
- Flank pain
- Sterile pyuria:
    - WBCs in urine
    - Routine cultures negative
    - Mycobacterial cultures positive

📌 Very high-yield sign

🔄 Latent vs Active Tuberculosis

- ~90% infections → Latent TB
- ~10% → Active TB
- Reactivation risk ↑ in:
  - AIDS
  - Diabetes
  - TNF-α blockers (e.g., infliximab)

📌 Untreated AIDS + TB → ~50% mortality

⚠️ Special Situation: IRIS

Immune Reconstitution Inflammatory Syndrome

- Seen in AIDS patients after starting HAART
- Rising $CD4^+$ T cells → exaggerated immune response
- Worsening TB symptoms despite therapy

📌 Management:

👉 Treat TB before initiating HAART

🔬 Laboratory Diagnosis

❑ Microscopy

Acid-Fast Staining

- Ziehl-Neelsen or Kinyoun stain 🔴
- Detects acid-fast bacilli in sputum

⚠️ Limitation:

- Sensitivity ~50%
- Many smear-negative cases are culture-positive

Fluorescent Staining

- Auramine-rhodamine stain 🌟
- Faster screening
- Higher sensitivity than ZN stain

2️⃣ Culture (Gold Standard 🏆)

- Specimen treated with:
  - NaOH (digestion)
  - Centrifugation

Media:

- Löwenstein–Jensen (egg-based)
- Middlebrook agar (synthetic)
- Growth time:
  - Up to 8 weeks

Liquid Culture (BACTEC)

- Detects radioactive CO_2 release
- Growth detected in ~2 weeks
- Faster & more sensitive

Biochemical Identification

- Niacin production → Positive ✅
- Catalase production → Positive ✅

3️⃣ Molecular Tests

NAATs

- Detect TB DNA / rRNA
- High specificity
- Best in smear-positive cases
- Allows early diagnosis & early treatment

Drug-Resistance Detection

- Gene mutations:
  - Catalase gene → INH resistance
  - RNA polymerase gene → Rifampin resistance

Luciferase Assay ✨

- Measures ATP production in presence of drug

Sensitive strain → Drug kills bacteria → ↓ ATP → ↓ Light

Resistant strain → Normal ATP → Normal light

4️⃣ Latent TB Diagnosis

PPD (Mantoux test)

- Type IV hypersensitivity
- Affected by BCG vaccination ❌

IGRA (Preferred in BCG-vaccinated)

- Tests:
  - QuantiFERON-TB Gold
  - T-SPOT.TB
- Measures IFN-γ release
- Not affected by BCG

- Cannot differentiate latent vs active TB

📌 Active TB must be ruled out with:

- Chest X-ray
- Sputum examination

💊 Treatment of Tuberculosis

🔹 General Principles

- Always multidrug therapy
- Duration: 6–9 months
- Non-infectious after 2–3 weeks of therapy

🔹 Standard Regimens (Pulmonary TB)

Classic Regimen

- INH + Rifampin → 6 months
- Pyrazinamide → first 2 months

Memory-Friendly Regimen

First 2 months → INH + Rifampin + Pyrazinamide + Ethambutol

Next 4 months → INH + Rifampin

Special Cases

- AIDS
- Disseminated TB
- Suspected INH resistance

→ All 4 drugs for 9–12 months

🔹 Latent TB Treatment

- INH → 6–9 months (preferred)
- INH + Rifapentine → 3 months
- Rifampin alone → INH-resistant exposure

⚠️ Never use Rifampin + Pyrazinamide

→ Severe hepatotoxicity

🔹 Monitoring

- INH-induced hepatitis risk ↑ after age 35
- Monitor LFTs

⚠️ Challenges in TB Therapy

Reasons for prolonged treatment:

1. Intracellular location
2. Caseous necrosis → poor drug penetration
3. Slow growth rate
4. Persister bacilli (metabolically inactive)

📊 Summary Table – Laboratory Tests

Test	Key Feature	Limitation
Acid-fast stain	Rapid	Low sensitivity
Auramine stain	Fluorescent, fast	Less specific
Culture (LJ/Middlebrook)	Gold standard	Very slow
NAAT	Rapid, specific	↓ sensitivity if smear-negative
IGRA	Not affected by BCG	Cannot differentiate
PPD	Cheap, common	BCG false positives

🔴 Drug Resistance in TB

MDR-TB

- Resistance to INH + Rifampin
- Common in AIDS patients
- Requires 4-5 drugs:
    - Ciprofloxacin
    - Amikacin
    - Ethionamide
    - Cycloserine

XDR-TB

- MDR-TB PLUS:
    - Fluoroquinolone resistance
    - Injectable drug resistance
- First identified in South Africa (HIV patients)

Bedaquiline

- Approved 2013
- Used for MDR-TB

- Inhibits ATP synthase
- Never used alone

Preventing Resistance

- Major causes:
  - Prior treatment
  - Noncompliance

📌 Best solution:
👉 DOT (Directly Observed Therapy)

🔄 Flowchart – Drug Resistance in TB

Initial TB infection → Inadequate therapy / Noncompliance → Survival of resistant mutants → MDR-TB (INH + Rifampin resistant) → Further mutations → XDR-TB (MDR + Fluoroquinolone + Injectable)

🛡️ Prevention

Core Strategies

- Early diagnosis & treatment
- Respiratory isolation
- Contact tracing
- Screening high-risk populations

Screening Indications

- HIV patients
- Close contacts
- Prisoners
- Drug users
- Alcoholics
- Immigrants from high-incidence countries

💉 BCG Vaccine

- Live attenuated *M. bovis*
- Prevents disease, not infection
- Most effective in children

⚠️ Not given to immunocompromised

📌 Special use:

- Bladder cancer immunotherapy

🥛 Other Preventive Measures

- Pasteurization of milk
- Eradication of infected cattle

✅ Ultimate Exam Pearls

- MDR-TB = INH + Rifampin resistance
- XDR-TB = MDR + Fluoroquinolone + Injectable
- DOT = best method to prevent resistance
- BCG = prevents disease, not infection

- Sterile pyuria = think renal TB

-> The End <-