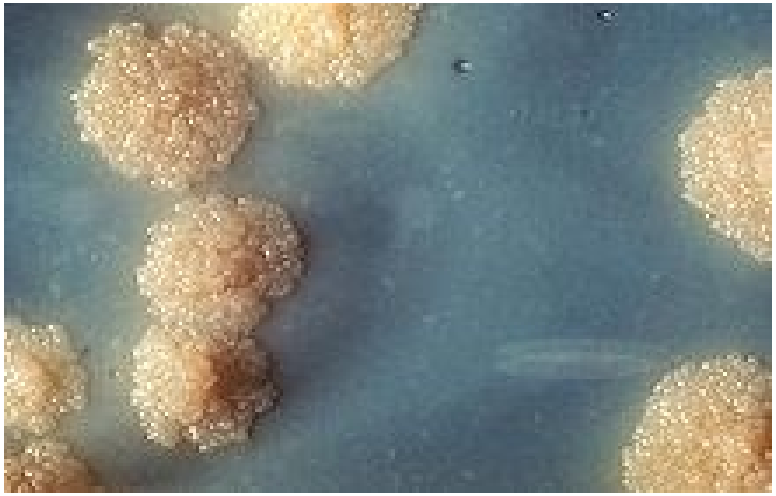
مرحبا .. الشابتر السابع بالمادة والأول من مادة السكند ، فرّغته صوت وكتابة ، ح تلاقوا شكل سماعة فوق عاليسار بكل سلايد 🔊 مجرد ما تضغطوا عليها ح يشتغل الشرح والشرح فعليًا أقل من دقيقة ، بس لازم تفتحوا الملف من ابليكيشن xodo

Artery Academy

Done By Mariam Yacoub



Antimycobacterial Drugs

Pharmacology 3

Dr. Heba Khader

ال **mycobacterium** بميزها تحت المايكروسكوب عن طريق إنها بتشكل **colonies** والها تصنيف خاص ومختلف عن ال **garm positive and negative** وطبعًا إلها **cell membrane** وخصائص مختلفة عن باقي أنواع البكتيريا

Mycobacteria

عندي **3species** من ال **mycobacterium** وهمة :

- *Mycobacterium tuberculosis*
  - Causes Tuberculosis ((السل
- *Mycobacterium leprae*
  - Causes Leprosy ((الجذام
- *Mycobacterium avium-intracellulare*
  - Atypical

بالنسبة للنوع التالت هو عبارة عن **complex** بين ال **avium @ intracellulare**
جمعناهم مع بعض لأنه **difficult to differntiation** مع العلم إنها تصنف **as atypical**
mycobacterium ومسؤولة عن كتير أمراض بتصيب الإنسان

- Mycobacterium avium complex (MAC) consists of two species: M avium and M intracellulare; because these species are difficult to differentiate, they are also collectively referred to as Mycobacterium avium-intracellulare (MAI) . MAC is the atypical Mycobacterium most commonly associated with human disease
- MAC is primarily a pulmonary pathogen that affects individuals who are immunocompromised

من هاي الأمراض هي الأمراض الرئوية **pulmonary pathogen** إلّي بتصيب الناس إلّي عندها ضعف وأمراض **immunocompromised** بالمناعة

Treatment of mycobacterial infection is complicated

الأسباب إلّي بتخليها تعمل **resistance** وهاد موضع اختلاف بينها وبين البكتريا هي:

- Mycobacteria are intrinsically resistant to most antibiotics. Because:
  1. they grow more slowly than other bacteria, antibiotics that are most active against rapidly growing cells are relatively ineffective.

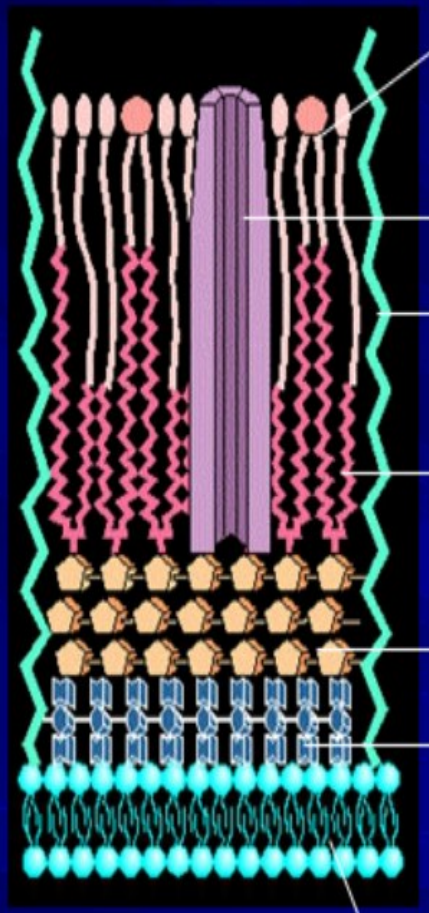
     بتنمو بشكل بطيء جدًا على عكس البكتريا إلّي بتنمو بشكل سريع ف بالتالي ما حيشتغل عليها ال **antibiotics**
  2. Mycobacterial cells can also be dormant and thus completely resistant to many drugs or killed only very slowly.

     بتضلها متجمعة بمكان معين بالخلايا وصعب يوصلها بعض ال **agent**
  3. The lipid-rich mycobacterial cell wall is impermeable to many agents.

     ال **cell wall** الها سمّيناه **mycolic acid** ومن هون اجت تسمية ال **mycobacterium**
     لإنه **lipid rich** ف بالتالي مش كل ال **agent** حتمُر من خلاله
  4. Mycobacterial species are intracellular pathogens, and organisms residing within macrophages are inaccessible to drugs that penetrate these cells poorly.
  5. mycobacteria are notorious for their ability to develop resistance.

     هالسبب بخليهم يضطروا انهم يستخدموا **combination** بين اكتر من دوا بنفس الوقت

Mycobacterial Cell Wall



Acyl lipid

Porin

Lipoarabinomannan(LAM)

Mycolates

Arabinoglycan

Peptidoglycan

Lipid Bilayer

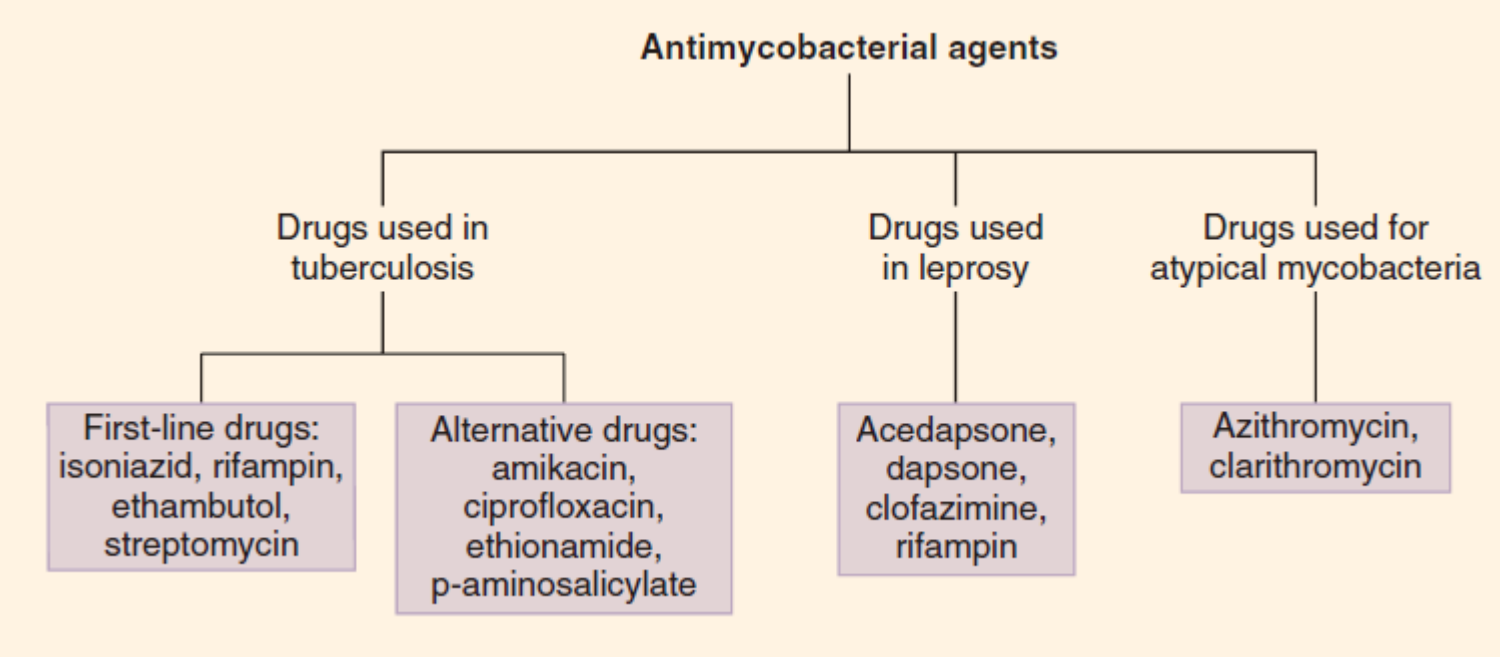
Treatment of mycobacterial infection is complicated

- Combinations of two or more drugs are required to overcome these obstacles and to prevent emergence of resistance during the course of therapy.
- The response of mycobacterial infections to chemotherapy is slow, and treatment must be administered for months to years, depending on which drugs are used.

لازم بالعلاج نستخدم نوعين أو أكتر من الأدوية لحتى هاي ال
mycobacterium ما تعمل **resistance** خلال فترة العلاج
وطبعًا استجابتها للعلاج جدًا بطيئة بتضل من أشهر لسنوات حسب
شو الأدوية إلّي استخدمتها بس أقل فترة علاج تقريبًا ٦ أشهر !

رح نقسم الشابتر لتلات أقسام حسب الأدوية إلّي بنستخدمها بعلاج ال **mycobacterial**

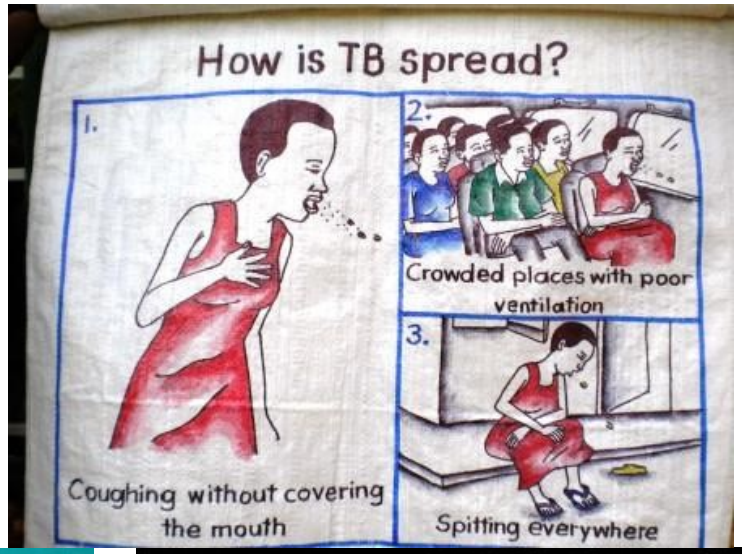
كالعادة عارفين شو ححكيلكم ، اعملولي سكيب عن هالسلايدة لحد ما نخلص الشابتر وبعدها بس نرجعلها ح يكون حفظها كتيير أسهل

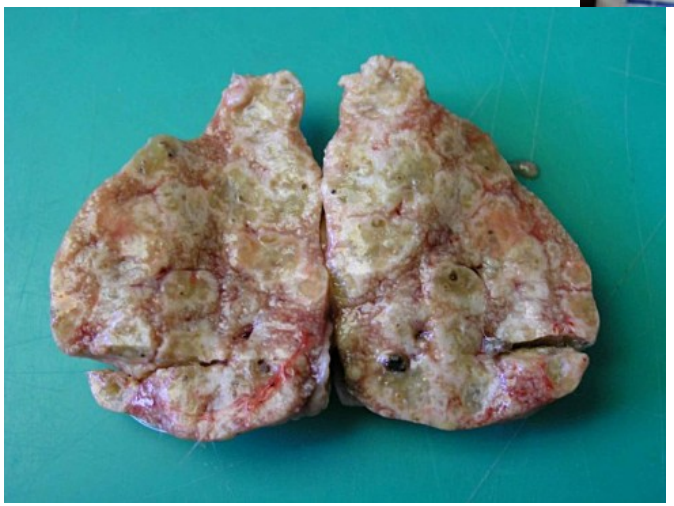


Tuberculosis =TB

- Mycobacterium tuberculosis causes serious infections to
  - Lungs (90% of the cases)
  - Genitourinary tract
  - Skeleton
  - Meninges

أول مرض من أمراض ال
mycobacterial هو ال **TB**
وإلّي حيأثر على هاي ال
organ : ورح نفصل عنهم
اكتر بالسلايدات الجاية





Tuberculosis

- Not everyone infected with TB bacteria becomes sick. As a result, two TB-related conditions exist: latent TB infection and TB disease.
- A person with latent TB may develop TB disease if he does not receive treatment.

إذا دخلت البكتيريا لجسم الإنسان وعملت **active disease** هاي بنسمّيها **TB disease**
أما إذا ضلت خاملة بالجسم وما عملت أي تأثير بنسمّيها **latent TB** مجرد ما قلت مناعة الشخص حيصيرلها **activation** وتتحول لل **TB disease**
لهيك إما بنعطي علاج لحتى نعالج المرض ، أو حماية إنه ما يصير **activation** أو وقاية من البكتيريا كلها أصلاً **prophylaxis**

A Person with Latent TB Infection	A Person with TB Disease
•Has no symptoms	•Has symptoms that may include • a bad cough that lasts 3 weeks or longer • pain in the chest • coughing up blood or sputum • weakness or fatigue • weight loss • no appetite • chills • fever • sweating at night
•Does not feel sick	•Usually feels sick
•Cannot spread TB bacteria to others	•May spread TB bacteria to others
•Usually has a skin test or blood test result indicating TB infection	•Usually has a skin test or blood test result indicating TB infection
•Has a normal chest x-ray and a negative sputum smear	•May have an abnormal chest x-ray, or positive sputum smear or culture
•Needs treatment for latent TB infection to prevent TB disease	•Needs treatment to treat TB disease

Drugs used in tuberculosis

- **Isoniazid (INH)**, **rifampin**, **pyrazinamide**, **ethambutol**, and **streptomycin** are the traditional five first-line agents for treatment of tuberculosis.

ال **second line** من العلاج بتميز إنه ممكن
يكون أقل **potent** أو اكتر **side effects**
وبنرجعله بس بحالة إنه ال **first line**
مش زابط استخدمه حاليًا **therapy**

ضروري جدًا تميزوا ال **first line therapy**

TABLE 47–1 Antimicrobials used in the treatment of tuberculosis.

Drug	Typical Adult Dosage[1]
First-line agents (in approximate order of preference)	
Isoniazid	300 mg/d
Rifampin	600 mg/d
Pyrazinamide	25 mg/kg/d
Ethambutol	15–25 mg/kg/d
Streptomycin	15 mg/kg/d
Second-line agents	
Amikacin	15 mg/kg/d
Aminosalicylic acid	8–12 g/d
Capreomycin	15 mg/kg/d
Ciprofloxacin	1500 mg/d, divided
Clofazimine	200 mg/d
Cycloserine	500–1000 mg/d, divided
Ethionamide	500–750 mg/d
Levofloxacin	500 mg/d
Rifabutin	300 mg/d[2]
Rifapentine	600 mg once or twice weekly

[1] Assuming normal renal function.

[2] 150 mg/d if used concurrently with a protease inhibitor.

Drugs used in tuberculosis

- An **isoniazid-rifampin combination** administered for 9 months will cure 95–98% of cases of tuberculosis caused by susceptible strains.
- The **addition of pyrazinamide** to an isoniazid-rifampin combination for the first 2 months **allows the total duration of therapy to be reduced to 6 months** without loss of efficacy.

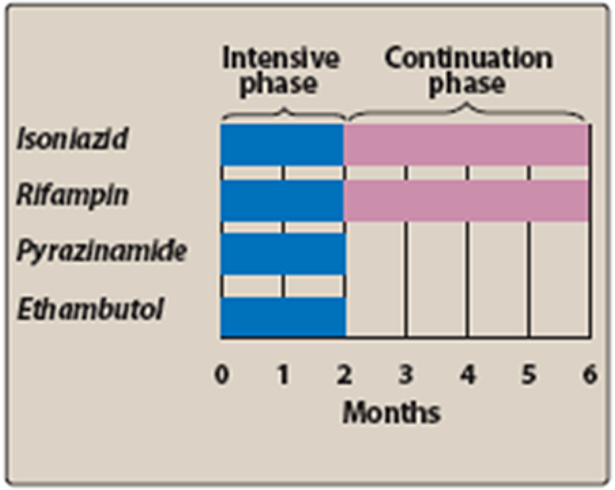


TABLE 47–2 Recommended duration of therapy for tuberculosis.

Regimen (in Approximate Order of Preference)	Duration in Months
Isoniazid, rifampin, pyrazinamide	6
Isoniazid, rifampin	9
Rifampin, ethambutol, pyrazinamide	6
Rifampin, ethambutol	12
Isoniazid, ethambutol	18
All others	≥ 24

isoniazid+rifampin=9month
isoniazid+rifampin+pyrazinamide=6 month
اقل فترة علاج هي ٦ اشهر واستخدامه لل pyrazinamide بكون فقط بأول شهرين من العلاج بما يسمى بال intensive phase وبعدين بصير يكمل عال combination لحاله

وهاد لا يعني لو ضفت دوا رابع حقلل فترة العلاج عن ٦ اشهر أكيد
ودور ال pyrazinamide وال ethambutol هون بكون بس إنه يقضوا عالبكتيريا أو ال strains إلّي ممكن تكون resistance لل combination بين ال isoniazid+ rifampin

Drugs used in tuberculosis

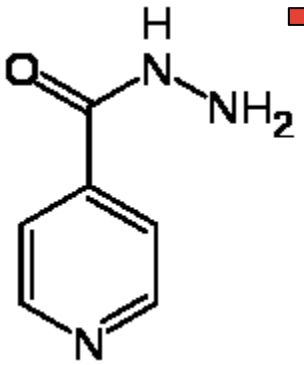
- In practice, therapy is usually initiated with a four-drug regimen of isoniazid, rifampin, pyrazinamide, and ethambutol until susceptibility of the clinical isolate has been determined.
- Neither ethambutol nor other drugs such as streptomycin adds substantially to the overall activity of the regimen (ie, the duration of treatment cannot be further reduced if another drug is used), but the fourth drug provides additional coverage if the isolate proves to be resistant to isoniazid, rifampin, or both.

استخدامنا للأدوية الأربعة سوا بالبداية بكون عشان أقلل ال **resistance** مش عشان أقلل فترة العلاج لأنه ما في أقل من ٦ أشهر

  - The prevalence of isoniazid resistance among clinical isolates in the United States is approximately 10%.
  - Prevalence of resistance to both isoniazid and rifampin (which is termed multidrug resistance) is about 3%.

الفرق بال **isoniazid resistance** لما كان لحاله ١٠٪ ولما كان مع **combination** صار ٣٪ بس !

Isoniazid (INH)



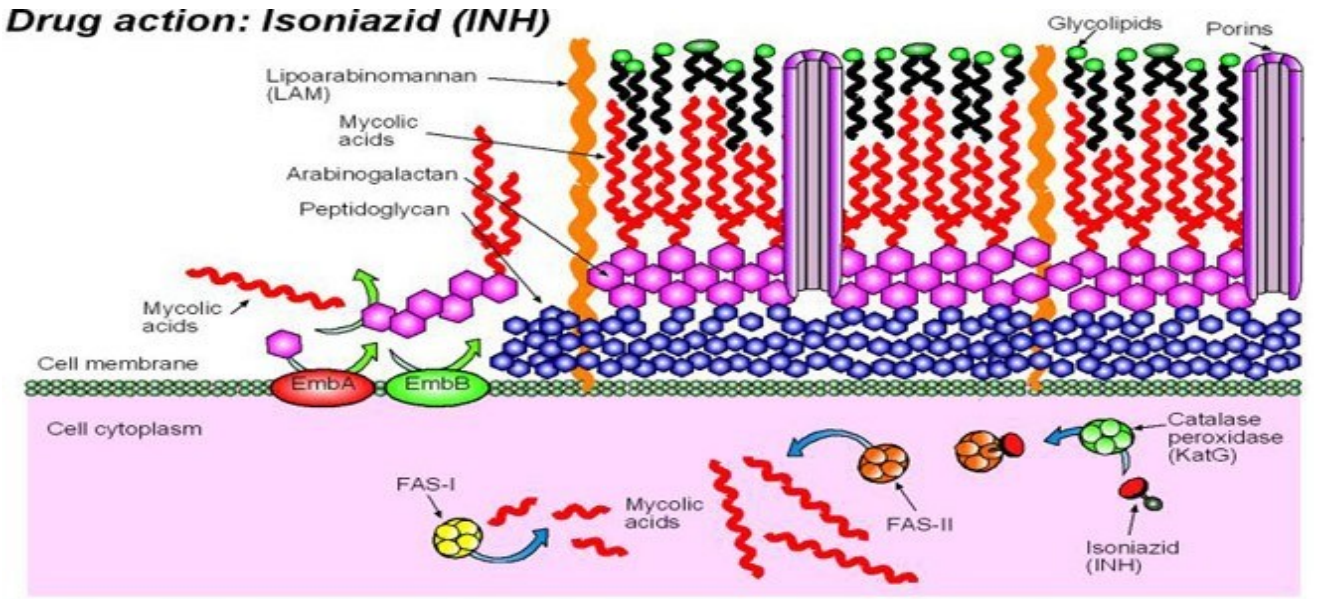
Treatment+Prophylaxis

- Isoniazid is the most active drug for the treatment of tuberculosis caused by susceptible strains.
- Should be used in combination to prevent emergence of resistance during therapy.
- Bactericidal to rapidly dividing mycobacteria,
- Used also as prophylaxis for all household members and very close contacts of patients with tuberculosis

أكتر دوا فعّال بعلاج ال **TB** وبقدر استخدمه ك **prophylaxis** في حال كان في شخص قريب مُصاب بال **TB** ، ما بستخدمه لحاله عشان ال **resistance** ولازم يكون ب **combination**
وأخر شي إنه **bactericidal not bacteriostatic**

Isoniazid (INH) MOA

- Isoniazid inhibits synthesis of mycolic acids, which are essential components of mycobacterial cell walls.
  1. Isoniazid is a prodrug activated by a mycobacterial catalase-peroxidase (KatG)
  2. Activated INH binds to and inhibits enoyl acyl carrier protein reductase (InhA)
  3. InhA is an essential component of fatty acid synthase complex (FAS II)
  4. FAS II is essential for synthesis of mycolic acid, an important component of mycobacteria cell wall



The first-line antibiotic drug isoniazid (INH) interferes with cell wall biosynthesis in Mycobacterium tuberculosis. INH is a prodrug and is converted to an active form by catalase peroxidase (KatG). Activated INH inhibits the action of enoyl-acyl carrier protein reductase (InhA). InhA is an important enzyme component of the fatty acid synthetase II (FAS-II) complex. FAS-II is involved in the synthesis of long-chain mycolic acids. Mycolic acids are essential structural components of the mycobacterial cell wall and are attached to the arabinogalactan layer.

immunopaedia.org

isoniazid prodrug ▶️ activation by KatG ▶️ active form bind and inhibition of InhA ▶️ InhA is essential component of FAS 2 ▶️ FAS2 essential for synthesis of mycolic acid ▶️ mycolic acid important component of mycobacterial cell wall

كيف ال mycobacterial حتعمل resistance ضد ال isoniazid

Resistance to INH

1. Mutation or deletion of KatG (producing mutants incapable of prodrug activation)بالتالي ال isoniazid ما حيتحوّل لل active form وما رح تصير العملية هاي كلها
2. Mutations resulting in overexpression of InhA.

- Drug-resistant mutants are normally present in susceptible mycobacterial populations at about 1 bacillus in 10^6. Since tuberculous lesions often contain more than 10^8 tubercle bacilli, resistant mutants are readily selected if isoniazid or any other drug is given as a single agent. The use of two independently acting drugs in combination is much more effective.

- At least two (or more) active agents should always be used to treat active tuberculosis to prevent emergence of resistance during therapy.

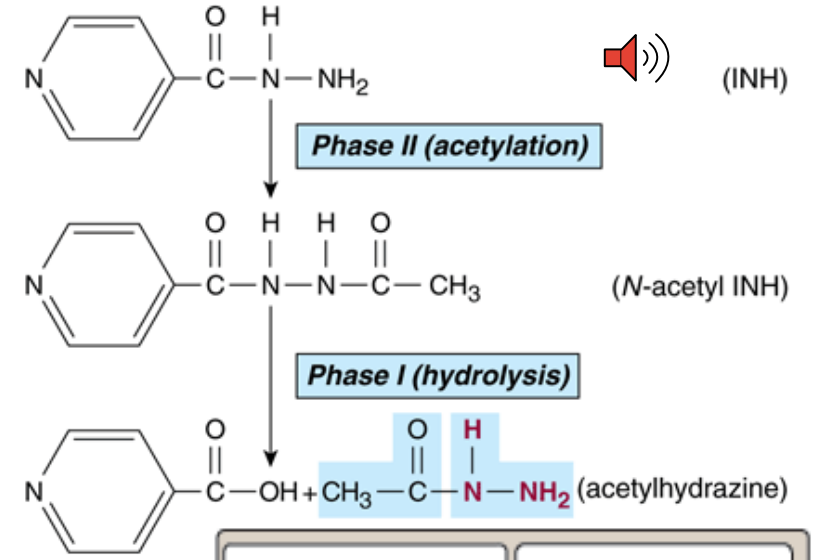
ما لازم المريض بال TB ياخد فقط isoniazid لإنه هيك حيقضي عال
mycobacterial isoniazid sensitive strains ورح تضل ال resistance
strains
لهيك لازم نعمل combination

Pharmacokinetics of INH

- Rapid oral absorption امتصاصهم سريع
- Carbohydrates, or aluminum-containing antacids impairs the absorption
  الكربوهيدرات وال **aluminum antacid** بإثروا ع امتصاصه
- Diffuses into all body fluids including the CSF.
  بصيرله **distribution** عالي
- The drug readily penetrates host cells and is effective against bacilli growing intracellularly. بقضي عال **bacilli** إلّي بتنمو داخل الخلايا
- Infected tissue tends to retain the drug longer.

Pharmacokinetics

- INH undergoes N-acetylation and hydrolysis, resulting in inactive products.
- A bimodal distribution of fast and slow acetylators exists. Native American are fast acetylators
- Isoniazid metabolites and a small amount of unchanged drug are excreted mainly in the urine.



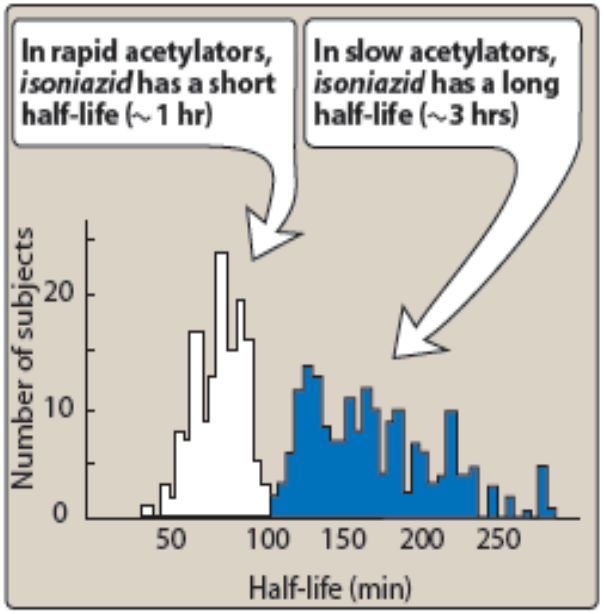


Figure 34 .4
Bimodal distribution of *isoniazid* half-lives caused by rapid and slow acetylation of the drug.

بخضع أول شي لل **phase 2** وهي ال **acetylation** وبعدها ال **phase 1** وهو ال **hydrolysis** وبعدها بصيرله **excretion in the urine**

حيتأثر بطبيعة الشخص إذا كان

rapid acetylators = Short half life

Slow acetylators= Long half life

زي ما بنشوف بال **bimodal curve**

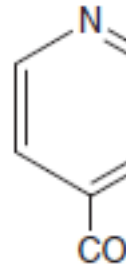
Clinical Uses

- The typical dosage of isoniazid is 5 mg/kg/d; a typical adult dose is 300 mg given once daily. Up to 10 mg/kg/d may be used for serious infections or if malabsorption is a problem.
- A 15 mg/kg dose, or 900 mg, may be used in a twice-weekly dosing regimen in combination with a second antituberculous agent (eg, rifampin, 600 mg).
- Isoniazid is usually given by mouth but can be given parenterally in the same dosage.
- Isoniazid as a single agent is also indicated for treatment of latent tuberculosis. The dosage is 300 mg/d (5 mg/kg/d) or 900 mg twice weekly, and the duration is usually 9 months.

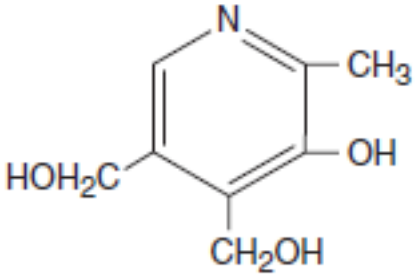
- ممكن أعطيه **300mg** جرعة يوميّة أو **900mg** مرتين أسبوعيًا وفترة العلاج بتضل ٩ أشهر
- بعطيه **oral** لكن ببعض الحالات ممكن أعطيه **parenteral**
- إذا كان ال **isoniazid** لحاله بستخدمه **prophylaxis and for latent TB**

Adverse effects of INH

- The incidence and severity of adverse reactions to isoniazid are related to dosage and duration of administration.
- Peripheral neuropathy is observed in 10–20% of patients given dosages greater than 5 mg/kg/d, but it is infrequently seen with the standard 300 mg adult dose.
  - More likely to occur in slow acetylators, diabetic, malnourished, or AIDS patients
  - Due to a relative pyridoxine deficiency (Isoniazid promotes excretion of pyridoxine).
  - Corrected by supplementation of 25 to 50 mg per day of pyridoxine (vitamin B6)
- Isoniazid-induced hepatitis is the most common major toxic effect.
  - The incidence increases among patients:
    - with increasing age,
    - who also take rifampin
    - who drink alcohol daily.
  - Development of isoniazid hepatitis contraindicates further use of the drug.



Isoniazid



Pyridoxine

من الأعراض الجانبية للـ isoniazid أول شي الـ peripheral neuropathy نتيجة الـ pyridoxine deficiency وهو vit B6
وبلاحظ وجود المشكلة أكتر عند الـ slow acetylators, diabetic, malnourished, or AIDS patients
الحل هون إني بعطي pyridoxine supplement لحتى أعوّض النقص عنده
تاني مشكلة الـ Hepatitis وبتزيد إذا المريض كان كبير بالعمر أو عم ياخد كحول بشكل يومي أو إذا بياخد الـ isoniazid+ rifampin ف بهاي الحالة لازم نعمل monitoring بشكل دائم
وأكيد مريض بال Hepatitis من البداية ما بعطيه isoniazid

Rifampin

- **Rifampin** (or **rifampicin**) is a semisynthetic derivative of rifamycin.
- Other rifamycin derivatives, eg, **rifabutin** and **rifapentine**.
- Resistant mutants are rapidly selected out if rifampin is used as a single drug, especially in a patient with active infection.
  - Must always be used in combination with at least one other antituberculosis drug to which the isolate is susceptible

ال rifampin يُعتبر ال first line therapy من ال rifamycin بينما ال rifabutin + rifapentine يُعتبروا second line therapy وبرجعلهم في حال كان مريض ايدز و TB بنفس الوقت وبدي اختار علاج يكون أقل drug drug interactions
وأكيد بتزيد ال resistance لما استخدمه لحاله لهيك لازم يكون combination مع كمان دوا واحد على الأقل من ادوية ال TB

Rifampin

MOA:

- Rifampin binds to the β subunit of bacterial DNA-dependent RNA polymerase and thereby inhibits RNA synthesis.
- Human RNA polymerase does not bind rifampin and is not inhibited by it.

beta subunits of bacterial DNA-dependent رح يرتبط بال
RNA polymerase ف بالتالي حيعمل **inhibition of RNA**
synthesis بدون ما يأثر عالإنسان

Resistance:

- Caused by a change in the affinity of the bacterial DNA-dependent RNA polymerase for the drug.
- Decreased permeability.

بتأثر ع موقع ارتباط ال **rifampin** أصلاً أو
بتمنع دخوله عن طريق تقليل ال
permeability

Rifampin Pharmacokinetics

- Absorption is adequate after oral administration.
- Distribution of rifampin occurs to all body fluids and organs
- Adequate levels are attained in the CSF only in the presence of meningeal inflammation.
- The drug is taken up by the liver and undergoes enterohepatic cycling.
- Elimination of metabolites and the parent drug is via the bile into the feces or via the urine

بينعطى **orally** وبصيرله **distribution** عالي خاصة لل
CSF لهيك بستخدمه بعلاج السحايا والدوا بيدخل لل
enterohepatic circulation وطبعًا بصيرله **eliminate**
شوي بال **urine** وبكمية أكبر بال **bile**

ممكن استخدمه لحاله أو مع أدوية تانية أو بديل لل **isoniazid** في حال إنه البكتيريا هاي كانت **resistance for isoniazid**

Rifampin Clinical Uses

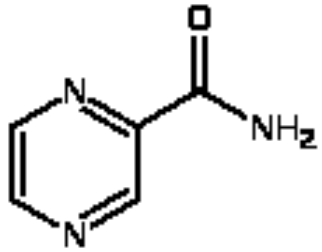
- **A. MYCOBACTERIAL INFECTIONS**
- Rifampin, usually 600 mg/d (10 mg/kg/d) orally, must be administered with isoniazid or other antituberculous drugs to patients with active tuberculosis to prevent emergence of drug-resistant mycobacteria.
- Rifampin, 600 mg daily or twice weekly for 6 months, also is effective in combination with other agents in some atypical mycobacterial infections and in leprosy.
- Rifampin, 600 mg daily for 4 months as a single drug, is an alternative to isoniazid for patients with latent tuberculosis who are unable to take isoniazid or who have had exposure to a case of active tuberculosis caused by an isoniazid-resistant, rifampin-susceptible strain.
- **B. OTHER INDICATIONS**
- eliminate meningococcal carriage.
- Prophylaxis in contacts of children with *Haemophilus influenzae* type b disease.

broad spectrum than isoniazid

Adverse effects

- Rifampin imparts a harmless orange color to urine, sweat, and tears (soft contact lenses may be permanently stained).
- Occasional adverse effects include rashes, thrombocytopenia, and nephritis.
- Rifampin may cause cholestatic jaundice and occasionally hepatitis.
- Rifampin strongly induces most cytochrome P450 isoforms (CYP1A2, 2C9, 2C19, 2D6, and 3A4), which increases the elimination of numerous other drugs.

Pyrazinamide

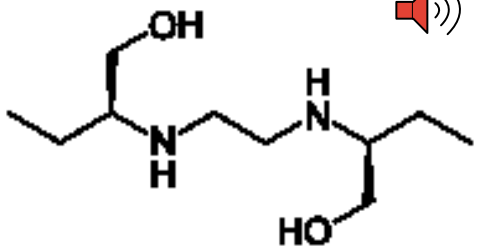


- Pyrazinamide is converted to pyrazinoic acid—the active form of the drug—by mycobacterial pyrazinamidase, which is encoded by *pncA gene*.
- Pyrazinoic acid disrupts mycobacterial cell membrane metabolism and transport functions.
- It is used only for treatment of tuberculosis.
- Resistance may be due to:
  - impaired uptake of pyrazinamide
  - mutations in *pncA* that impair conversion of pyrazinamide to its active form.
- The drug is taken up by macrophages and exerts its activity against mycobacteria residing within the acidic environment of lysosomes.
- Pyrazinamide is an important front-line drug used in combination with isoniazid and rifampin in short-course (ie, 6-month) regimens as a “sterilizing” agent active against residual intracellular organisms that may cause relapse.

- S/E:
  - Urate excretion is decreased (gout may be exacerbated) but no need to halt the therapy when it occurred.
  - Hepatotoxicity (in 1–5% of patients)

ال pyrazinamide ح يتحول لل active form وهو ال pyrazinoic acid عن طريق إنزيم ال mycobacterial pyrazinamidase إلّي هو encoded by PncA gene
بستخدمه بعلاج ال TB ولما يكون موجود مع combination of anti TB drug رح يقللي فترة العلاج زي ما حكينا قبل
ال resistance اما بتكون عن طريق impaired uptake of pyrazinamide أو بعمل mutation بالإنزيم المسؤول عن تحويله لل active form وهو ال PncA gene
أهم ساید ایفیکت إله رح احط علیها هایلایتر

Ethambutol



- It disrupts arabinogalactan synthesis by inhibiting arabinosyl transferases which are encoded by the emb gene.
- As with all antituberculous drugs, resistance to ethambutol emerges rapidly when the drug is used alone. Therefore, ethambutol is always given in combination with other antituberculous drugs.
- Resistance involves mutations resulting in overexpression of emb gene products.
- Well distributed throughout all the body
- Excreted by glomerular filtration and tubular secretion, need dose adjustment in renal failure.
- S/E:
  - Optic neuritis (inflammation of optic nerve): which leads to diminished visual acuity and ability to discriminate between red and green objects.
    - Dose-dependent
    - Reversible upon drug discontinuation
    - Ethambutol is relatively contraindicated in children too young to permit assessment of visual acuity and red-green color discrimination.

Streptomycine

- The mechanism of action and other pharmacologic features of streptomycin are discussed with **aminoglycosides.**
- Streptomycin penetrates into cells poorly and is active mainly against extracellular tubercle bacilli.
- Streptomycin sulfate is used when an injectable drug is needed or desirable and in the treatment of infections resistant to other drugs.

يُعتبر **amino glycosides** ورح أعطيه لل **extracellular bacilli** لإنه
ال **penetration** إله قلييل على عكس الباقي
وزي ما حكينا هو ال **iv** من ال **first line therapy** وبرجعله في حال
كانت ال **strains** هي **resistance** لباقي الأدوية

Alternate second-line drugs for TB

- **Para-aminosalicylic acid, ethionamide, cycloserine, capreomycin, fluoroquinolones, aminoglycosides and macrolides**
- Second line because they are either
  - No more effective than the first-line agents and their toxicities are often more serious, or
  - They are particularly active against atypical strains of mycobacteria.

Capreomycin

ال **second line therapy** مش فعال اكتر من ال **first line** زي ما حكينا قبل
بس بنستخدمهم بحالة ال **atypical strains of mycobacterial**

- A peptide that inhibits protein synthesis
- Administered parenterally (IM)
- Reserved for the treatment of multidrug-resistant tuberculosis
- Careful monitoring of the patient is necessary to prevent its **nephrotoxicity** and **ototoxicity**. **side effects :**

Ethionamide

- Ethionamide is chemically related to isoniazid and similarly blocks the synthesis of mycolic acids.
- It is effective after oral administration and is widely distributed throughout the body, including the CSF
- S/E: gastric irritation, hepatotoxicity, peripheral neuropathies, and optic neuritis
- Supplementation with vitamin B6 (pyridoxine) may lessen the severity of the neurologic side effects.

Para-aminosalicylic Acid

- Aminosalicylic acid (structurally similar to p-amino-benzoic acid (PABA) and to the sulfonamidesis) is a folate synthesis antagonist that is active almost exclusively against *M tuberculosis*.

Fluoroquinolones: ciprofloxacin, moxifloxacin and levofloxacin

Macrolides: Azithromycin and clarithromycin

- Azithromycin is preferred for HIV-infected patients because it is least likely to interfere with the metabolism of antiretroviral drugs.

ال ethionamide بشبه بالستركشر لل isoniazid حتى نفس طريقة شغله عال
mycolic acid بس صنّفناه بال second line بسب السايد ايفيكت الكتيرة تبعته
وحطيتلكم عليها هايلايتر وبنفس الطريقة بنعطي pyridoxine supplement

ال para amino salicylic acid بشبه ال PABA ف بشتغل folate synthesis
antagonist وكمان فعّال عال M tuberculosis

ال floroquinolones حكينا عنهم كتير
وأخر شي ال macrolides زي ال azithromycin and clarithromycin
وبفضّل ال azithromycin بحال إذا كان الشخص مصاب بال HIV وال TB بذات
نفس الوقت عشان يكون اقل interaction

Leprosy (Hansen's disease)

- Caused by M. leprae
- Symptoms include granulomas of the nerves, respiratory tract, skin, and eyes. This result in a lack of ability to feel pain and weakness and poor eyesight may also be present. Skin lesions are the primary external sign.
- Bacilli from skin lesions or nasal discharges of infected patients enter susceptible individuals via abraded skin or the respiratory tract
- The WHO recommends combination of **dapsone**, **clofazimine**, and **rifampin** for 6 to 24 months

من أهم الأعراض هي **granulomas** في الأعصاب والريس والسكين والعين وببطل قادر يشعر بالألم والضعف وحتى بصيبه ضعف البصر ولكن اهم عَرَض خارجي ممكن الاحظه هو ال **skin lesions** وبعالجه عن طريق ال **dapsone , clofazimine , rifampin** لمدة ٦-٢٤ شهر

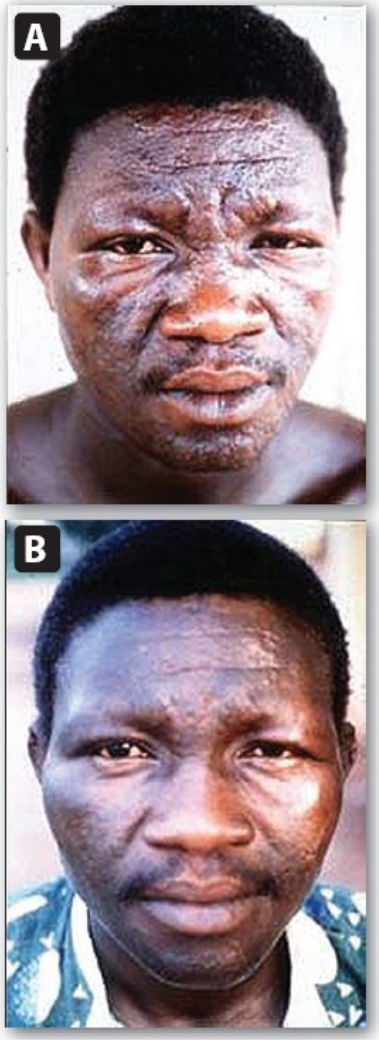
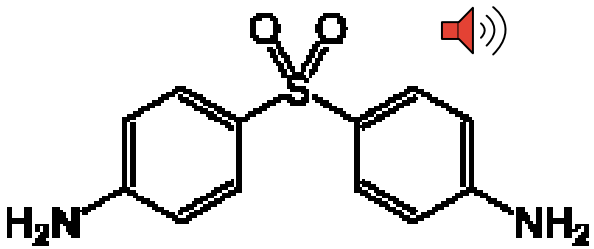


Figure 34.13
Leprosy patient. A. Before therapy. B. After 6 months of multidrug therapy.

Leprosy Treatmer



Dapsone

- Structurally related to the sulfonamides
- Inhibits folate synthesis via dihydropteroate synthetase inhibiton
- Dapsone is also employed in the treatment of pneumonia caused by Pneumocystis jiroveci in patients infected with HIV
- The drug is well absorbed from the gastrointestinal tract and is distributed throughout the body, with high levels concentrated in the skin
- Enters the enterohepatic circulation and undergoes hepatic acetylation
- Both parent drug and metabolites are eliminated through the urine

Clofazimine

- Binds to DNA and prevents it from serving as a template for future DNA replication
- Bactericidal to M. leprae and has some activity against M. avium-intracellulare complex

برتبط بال **DNA** وبمنع ال **DNA replication**
وبشتغل **bactericidal** بعلاج **species 2** من ال **mycobacterial** وهمة
ال **leprae + MAC**

The End