आईएफटीएम विश्वविद्यालय, मुरादाबाद, उत्तर प्रदेश

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NAAC ACCREDITED

E-Content

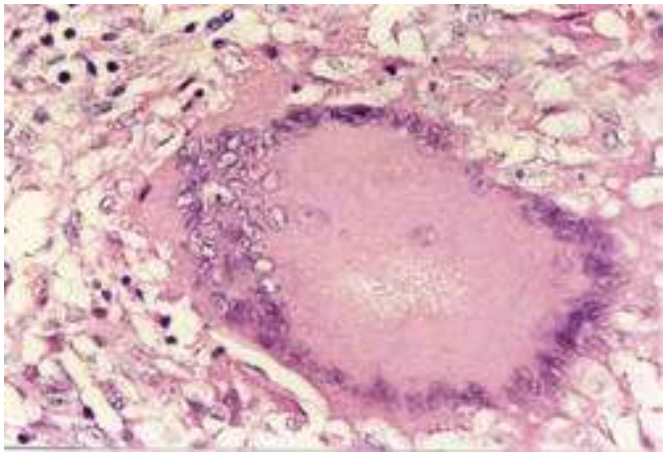
IFTM University, Moradabad

Antitubercular Agents

Antitubercular Agents

- Tuberculosis is a chronic granulomatous disease
- In developing countries it is a major health problem
- ≈ 30% of world population is infected with Myc. tuberculosis infection
- In India > 2 million people develop active disease every year & half million die.

Tuberculosis



Mycobacterium tuberculosis

It is an infection difficult to treat

??

Typical growth characteristics

Peculiar cell wall structure **-**(waxy appearance) due to **mycolic acid.**

Resistance to infection emerges quickly.

Antitubercular Drugs
Mycobacterium Infections

Common infection sites

- Lung (primary site)
- Brain
- Bone
- Liver
- Kidney
- Intestines
- Lymph nodes

- **Aerobic bacillus**
- **Passed from infected:**
  - Humans
  - Cows (bovine) and birds (avian)
    - Much less common

Antitubercular Drugs *Mycobacterium* Infections

- Tubercle bacilli are **conveyed by droplets**
- Droplets are expelled by **coughing or sneezing,** then gain entry into the body by **inhalation**
- Tubercle bacilli then **spread to other body organs via blood and lymphatic systems**
- Tubercle bacilli **may become dormant**,

Antitubercular Drugs
Tuberculosis - Pathophysiology

- ***M. tuberculosis*** – gram-positive, acid-fast bacillus

- **Spread from person to person via airborne droplets**
  - Coughing, sneezing, speaking – disperse organism and can be inhaled
  - ***Cannot be spread by hands, books, glasses, dishes, or other fomites***

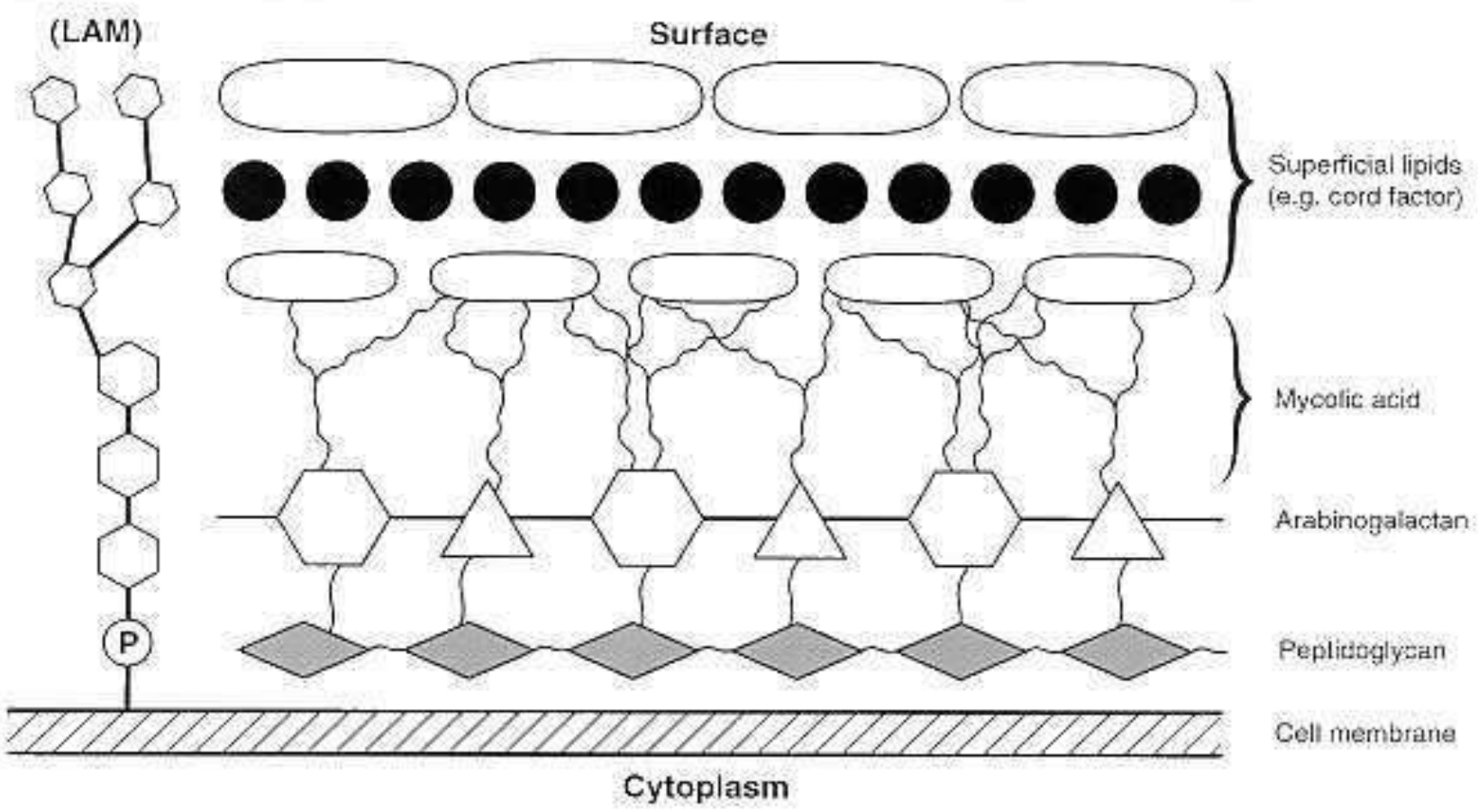
Antitubercular Drugs
Tuberculosis – Clinical Manifestations

- **Early stages** – free of symptoms
  - Many cases are found incidentally
- **Systemic manifestations**:
  - Fatigue, malaise, anorexia, weight loss, low-grade fevers, night sweats
  - Weight loss – occurs late
  - Characteristic cough – frequent & produces mucoid or mucopurulent sputum
  - Dull or tight chest pain
- **Some cases**: acute high fever, chills, general flulike symptoms, pleuritic pain, productive cough

Tuberculosis – Diagnostic Studies

- **Tuberculin Skin Testing** -- + reaction 2-12 weeks after the initial infection
  - **PPD** – Purified protein derivative – used to detect delayed hypersensitivity response
    - Two-step testing – health care workers
    - 5mm > induration – Immunosuppressed patients
    - 10 mm> "at risk" populations & health care workers
    - 15 mm> Low risk people
  - **Chest X-ray** -- used in conjunction with skin testing
    - Multinodular lymph node involvement with cavitation in the upper lobes of the lungs
    - Calcification – within several years after infection
  - **Bacteriologic Studies** –
    - Sputum, gastric washings –early morning specimens for acid-fast bacillus -- three consecutive cultures on different days
    - CSF or pus from an abscess

Mycobacterial cell wall



Baron S (ed.) Medical Microbiology. 4th edition. Chapter 33

Chemotherapy in tuberculosis

- **Goals of anti-tubercular chemotherapy**

***Kill dividing bacilli*:** Patient is non-contagious : transmission of TB is interrupted.

***Kill persisting bacilli*:** To effect cure and prevent relapse.

Prevent emergence of resistance: so that the bacilli remain susceptible to the drugs.

Antitubercular Agents

- Now there is emergence of multidrug resistant (MDR) TB . More than 0.4 million cases globally .

History

- First successful drug for treating TB was

  PAS (Para- aminosalicylic acid) developed by **Lehman in 1943**.

- Dramatic success came when…..

Antitubercular Agents

Waksman & Schutz discovered Streptomycin which has made remarkable progress.

- Followed by **Thiacetazone** by **Domagk** in in 1946
- In 1952 **Isoniazid** came into being
- **Pyrazinamide** by **Kushner & colleagues** in 1952 & later on **Rifampicin** in 1957 by **S. Margalith** has totally changed the strategy in the chemotherapy.

Antitubercular Agents

- Ethambutol came in 1961 by **Lederle - laboratories**
- Fluoroquinolones , newer macrolides & congener of Rifampicin →Rifabutin are recent addition in antimycobacterial drugs

Drugs used in Tuberculosis

1st line drugs high efficacy, low toxicity	2nd line drugs Low efficacy, high toxicity or both
• Isoniazid (INH) • Rifampin • Pyrazinamide • Ethambutol • Streptomycin	• Ethionamide • Para aminosalicylic acid • Cycloserine • Amikacin/ Capreomycin • Fluoroquinolones • Rifabutin

Antitubercular Agents

First line drugs:

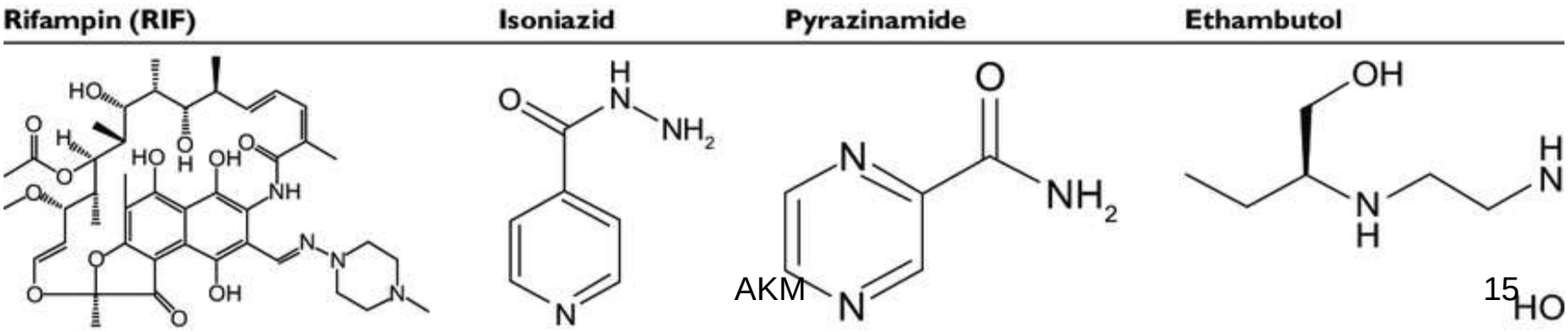
Ionizid (H)

Rifampicin (R)

Ethambutol (E)

Pyrazinamide (Z)

Streptomycin (S) **now reserved drug in first line**



Antitubercular Agents

Second line drugs:

Thiacetazone

Para aminosalicylic acid (PAS)

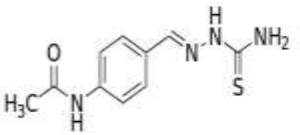
Ethionamid

Kanamycin

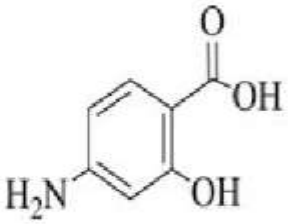
Cycloserine

Amikacin

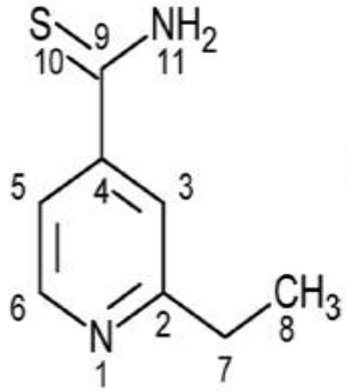
Capreomyc



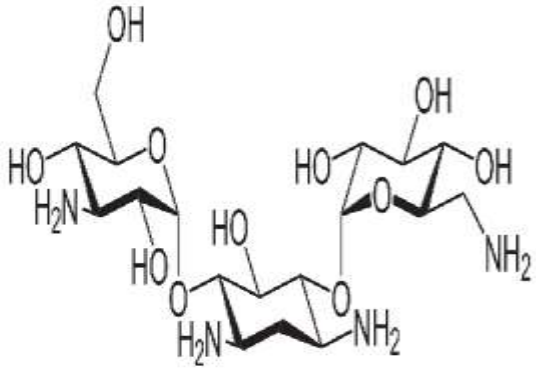
Thiacetazone



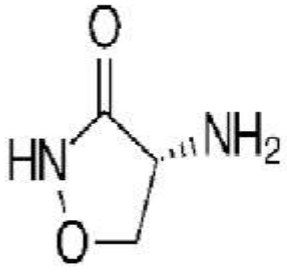
p-aminosalicylic acid



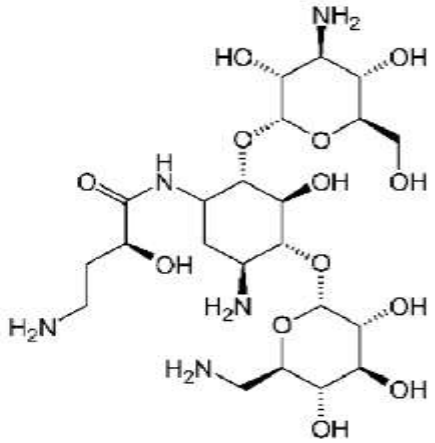
Ethionamide



Kannamycin



Cycloserine



Amikacin

Antitubercular Agents

Newer Second Line drugs:

Ciprofloxacin

Ofloxacin

Levofloxacin

Clarithromycin

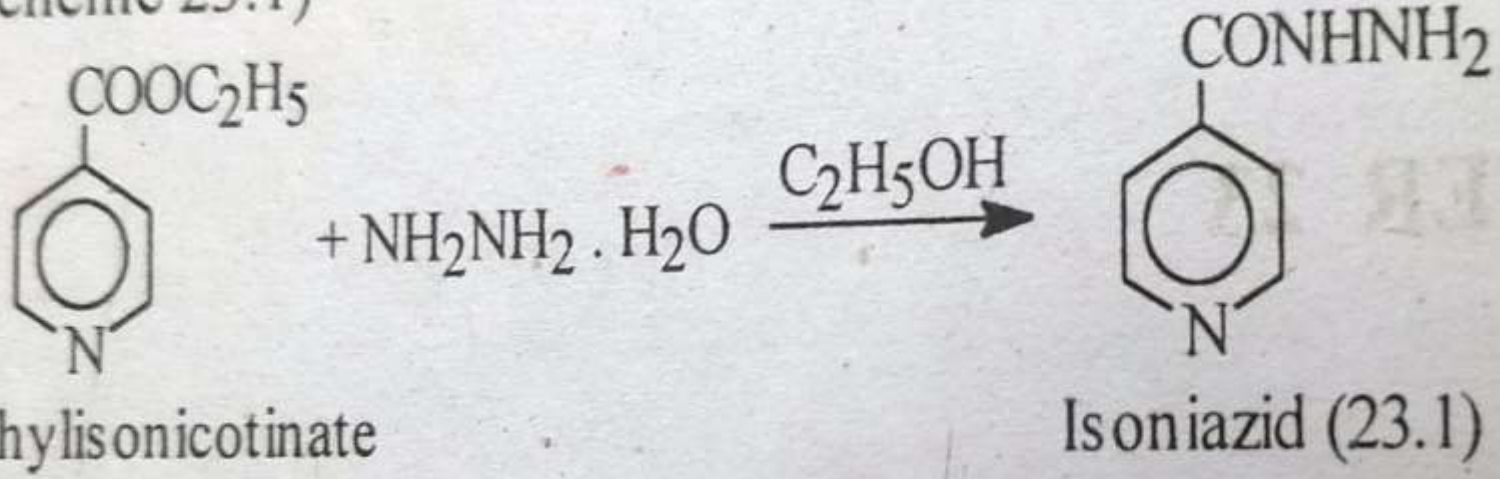
Azithromycin

Rifabutin

SYNTHESIS ---INH

Isoniazid (INH) (Laniazid) I.P. : 4-Pyridinecarboxylic acid hydrazide (23.1).

Synthesis (Scheme 23.1)



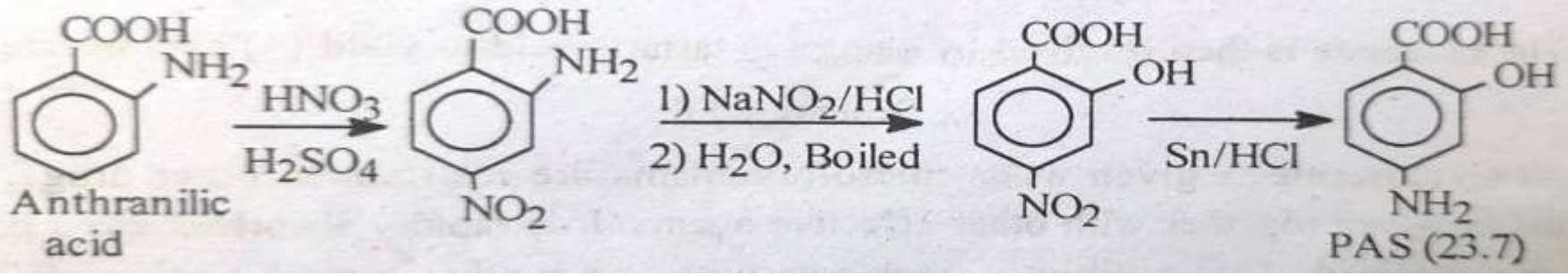
Ethylisonicotinate

Isoniazid (23.1)

SYNTHESIS--PAS

p-Aminosalicylic Acid (PAS) : (Tubacin); 4-Amino-2-hydroxy benzoic acid (23.7)

Synthesis : (Scheme 23.7)



Antitubercular Agents

Isoniazid (Isonicotinic acid hydrazide,H):

Essential component of all anti TB regimen (except intolerance to H or resistance)

-It is tuberculocidal , **kills fast multiplying organism** & inhibit slow acting organism

-Acts both on intracellular (present in macrophages) & extracellular bacilli

-It is the cheapest AT Agent

- **Pyridine Derivative**

Antitubercular Agents

-Atypical mycobacteria are not inhibited by **INH**.

Not active against any other micro-orgs.

Mechanism of Action :

Inhibit synthesis of **mycolic acid** (unique fatty acid component of mycobacterial cell wall .)

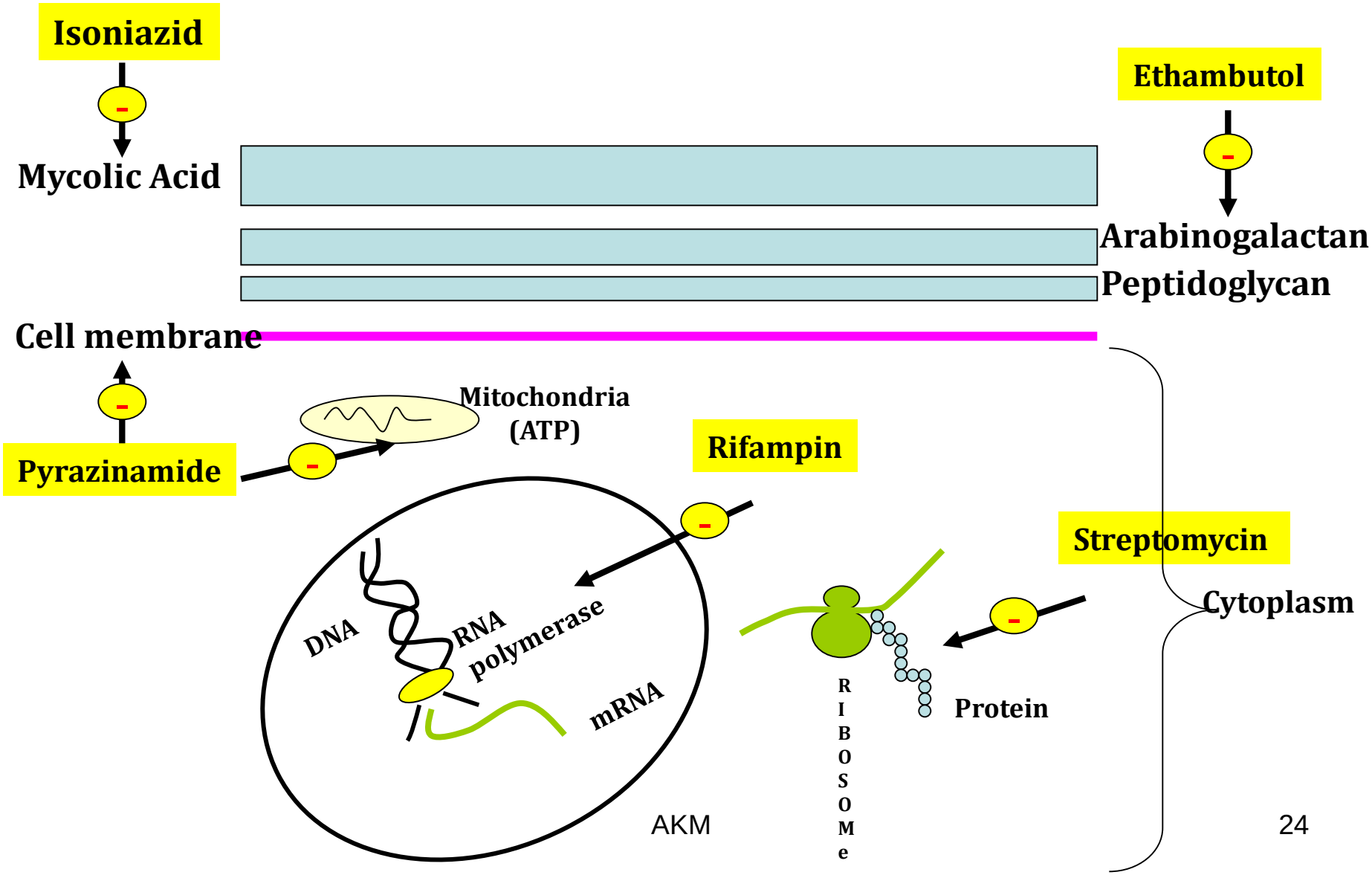
Antitubercular Agents

-INH enters the bacilli by passive diffusion. It must be activated to become toxic to bacilli. It became toxic by **Kat G** (multifunctional Catalase - peroxidase , a bacterial enzyme) which catalyzes the product from INH an **Isonicotinoyl radical** that subsequently inter-acts with mycobacterial NAD & NADP to produce dozen of adducts , one of these

Antitubercular Agents

a nicotinoyl NAD isomer which ↓ the activity of **enoyl acyl carrier protein reductase** (**Inh A**) & **β- ketoacyl carrier protein synthase** (**Kas A**) , inhibition of these enzymes↓ the synthesis of mycolic acid an essential component of the mycobacterial cell wall & causes cell death.

MOA of 1st line drugs



Antitubercular Agents

Pharmacokinetics :

-Completely absorbed orally , penetrate all body tissues, tubercular cavities , placenta & meninges .

- Metabolized in liver by **acetylation** & metabolites are excreted in urine .
- Rate of acetylation shows genetic variation

(**fast acetylators > 30% Indians - t½ -1 hr**

Slow acetylators >60% Indians -t ½- 3 hrs)

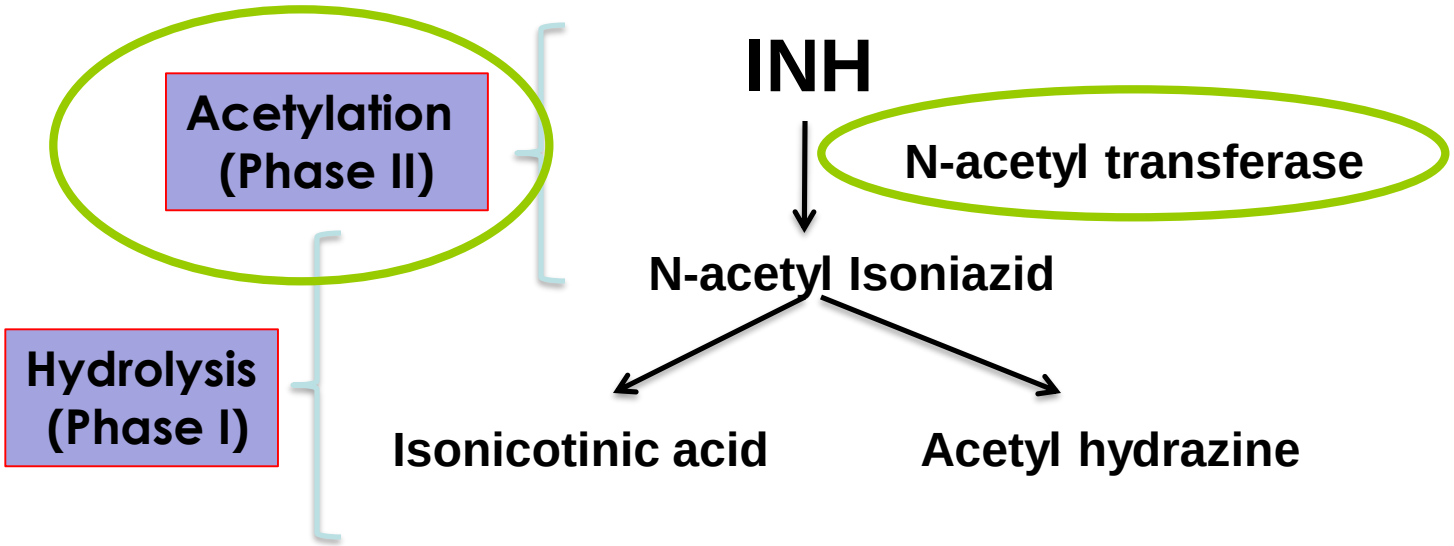
Antitubercular Agents

(daily regimen is not affected but biweekly regimens are less effective in fast acetylators)

Dose – 4-6 mg/ kg for >50 kg – 300 mg daily

- 600 mg bi-wkly

ISONIAZID (INH): Pharmacokinetics



Genetic polymorphism affects INH metabolism

Slow acetylators are at higher risk of developing neuritis

Antitubercular Agents

ADRs -

Well tolerated drug

1.Peripheral neuritis & other neurological manifestations- parasthesia , numbness, mental disorientation & rarely convulsion

(**due to interference with utilization of pyridoxine & ↑ excretion in urine**)

Antitubercular Agents

Due to this Pyridoxine given prophylactically

-**10 mg/day** which prevents neurotoxicities

(INH **neurotoxicity** treated with Pyridoxine-**100 mg/ day**)

2. Hepatitis – more common in older patients & alcohlics (reversible)

3. Rashes , fever , acne & arthralgia .

Antitubercular Agents

Rifampin (Rifampicin , R):

-Semisynthetic derivative of Rifamycin B from **Streptomyces mediterranei**

-Bactericidal to M. Tuberculosis & others –

S. aureus
N. meningitidis
H. influenzae
E. coli
Klebsiella
Pseudomonas
Proteus
& Legionella

Antitubercular Agents

- Best action on **slowly or intermittently dividing bacilli on extracellular as well as intracellular organisms**

-Also act on many atypical mycobacteria

-Have good resistance preventing action

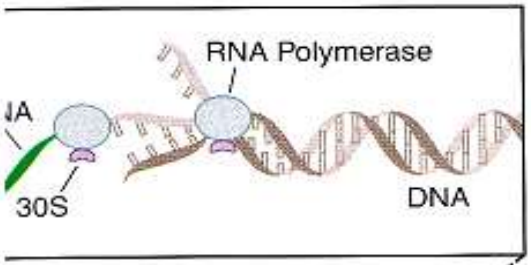
Antitubercular Agents

Mechanism:

Inhibit DNA dependant RNA Synthesis

(by ↓ **bact RNA polymerase** , selective because does not ↓ mammalian RNA polymerase)

- TB patient usually do not get primary Rifampicin resistance – If occurs is due to mutation in the repo -B gene (β subunit of RNA polymerase).
- No cross resistance



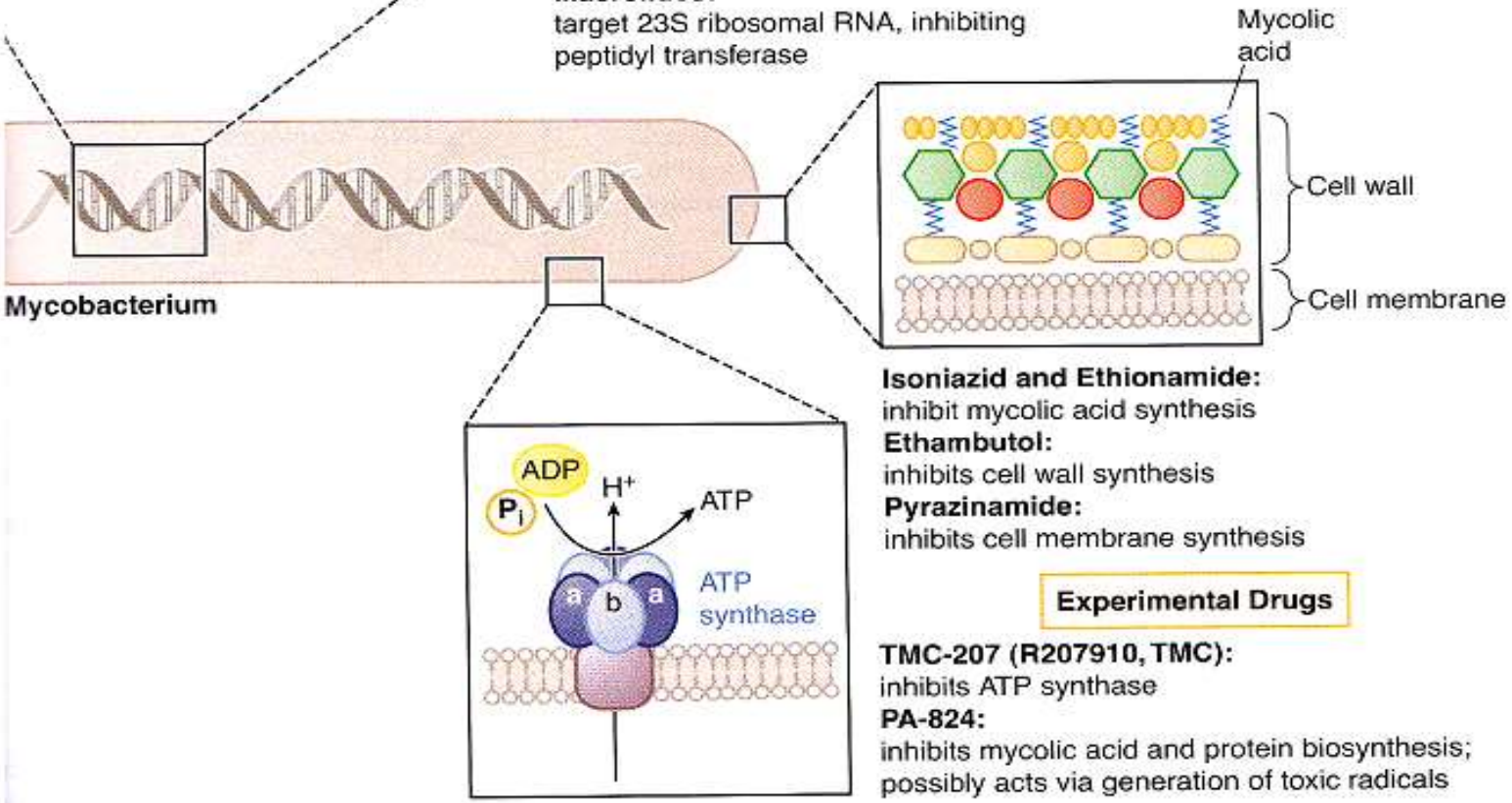
Approved Drugs

Fluoroquinolone:
inhibits DNA synthesis and supercoiling by targeting topoisomerase

Rifamycin:
inhibits RNA synthesis by targeting RNA polymerase

Streptomycin:
inhibits protein synthesis by targeting the 30S ribosomal subunit

Macrolides:
target 23S ribosomal RNA, inhibiting peptidyl transferase



Isoniazid and Ethionamide:
inhibit mycolic acid synthesis

Ethambutol:
inhibits cell wall synthesis

Pyrazinamide:
inhibits cell membrane synthesis

Experimental Drugs

TMC-207 (R207910, TMC):
inhibits ATP synthase

PA-824:
inhibits mycolic acid and protein biosynthesis; possibly acts via generation of toxic radicals

Mechanisms of action of established and experimental drugs used for the chemotherapy of mycobacterial infections. Shown

Antitubercular Agents

PKT –

Well absorbed orally widely distributed in the body , penetrate cavities , **caseous mass**, placenta & meninges .

-Metabolized in liver

-Excreted mainly in bile & some in urine

-t½- 2-5 hrs

Antitubercular Agents

ADR's

1. **Hepatitis** – mainly in pts having preexisting liver disease & is dose related- Jaundice req. stoppage of drug
2. **Respiratory syndrome** –breathlessness shock & collapse .
3. Purpura , hemolysis , shock , renal failure

Antitubercular Agents

4. **Cutaneous syndrome** – flushing , pruritis & rashes (face & scalp), redness & watering of eyes.
5. **Flue syndrome** – Nausea , vomiting, abdominal cramps

(**Urine & secretions may become red – which are harmless & Pt should be told about this effect**)

Antitubercular Agents

3. **Pyrazinamide (Z)**

Chemically≡ INH

-Weak tuberculocidal more active in acidic medium

-More lethal to intracellular bacilli & to those at sites showing an inflammatory response

(Therefore effective in first two months of therapy where inflammatory changes are present)

Antitubercular Agents

-Good sterilizing activity

-It's use enabled total duration of therapy to be shortened & risk of relapse to be reduced.

Mechanism ≡ INH - ↓ fatty acid synthesis but by interacting with a different fatty acid synthesis encoding gene .

Antitubercular Agents

PZA is thought to enter M. tub. by passive diffusion and converted to **pyrazinoic acid** (its active metabolite) by bact. pyrazinamidase enz. .This metabolite inhibits mycobact. fatty acid synthase -I enz. and disrupts mycolic acid synthesis needed for cell wall synthesis

Antitubercular Agents

PKT :

-Absorbed orally, widely distributed ,Good penetration in CSF.

-Metabolized in liver & excreted in urine.

-t½ -6-10 hrs

Antitubercular Agents

ADRs :

-Hepatotoxic -dose related

-Arthralgia , hyperuricaemia, flushing , rashes , fever & anaemia

-Loss of diabetic control

Dose – 20-30 mg /kg daily , 1500 mg if > 50 kg

Antitubercular Agents

Ethambutol (E) :

-Tuberculostatic , clinically active as Streptomycin

-Fast multiplying bact.s are more sensitive

-Also act against atypical mycobacteria

-If added in triple regimen (RHZ) it is found to hasten the rate of sputum conversion & to prevent development of resist.

Antitubercular Agents

Mech. :

Not well understood . Found to ↓arabinosyl transferase III involved in arabinogalactone synthesis & also interfere with mycolic acid incorporation in mycobacterial cell wall (**this is encoded by emb AB genes**)

-Resistance develop slowly

- No cross resistance

Antitubercular Agents

PKT:

-3/4th of an oral dose of **Ethm**. is absorbed

-Distributed widely but penetrates in meninges incompletely

-½ metabolized , excreted in urine

-caution is required in pts of renal disease

-Pts acceptability is good & S/Es are low

Antitubercular Agents

ADRs:

-**Loss of visual acquity / color vision due to optic neuritis** ,which is most impt. dose & duration dependent toxicity.

(**children can not report this complaint easily therefore not given below 6 yrs of age**)

-Early recognition –reversible

Others- Nausea , rashes & fever

Antitubercular Agents

-Neurological changes

-Hyper uricaemia is due to interference with urate excretion

Dose – 15-20 mg/kg , > 50kg -1000mg

Antitubercular Agents

Streptomycin (S):

-It was 1st clinically useful antibiotic drug

-It is protein synthesis inhibitor by combining with **30S ribosome**

-It is **tuberculocidal** , but less effective than INH / Rifampicin

-Acts on **extracellular bacilli only** (poor penetration in the cells)

Antitubercular Agents

-It penetrates tubercular cavities but **does not cross BBB**

- Resistance when used alone

- Atypical mycobact.s are ineffective

- Popularity ↓ due to need of IM inj. & lower margin of safety (because of ototox. & nephrotox.).

- **Dose- 15 (12-18) mg/kg, >50 mg- 1000mg**

Antitubercular Agents

Thiacetazone (TZN) :

-First AT drug tested but weak

-Discarded due to hepatotoxicity

-In India revived in 1960s for oral use along with INH as a substitute to PAS

Antitubercular Agents

-Tuberculostatic , does not add to the therapeutic effect of H,S, R, E

ADRs -

Hepatotoxic

Exfoliative dermatitis

Stevenson Johnson's syndrome

Can cause bone marrow depression

Others- Nausea , anorexia , abd. discomfort

Antitubercular Agents

Loose motions

Mild anemia

Pruritis

Dose- 150 mg OD (2-5 mg/ kg) ,used in combined tablet with INH

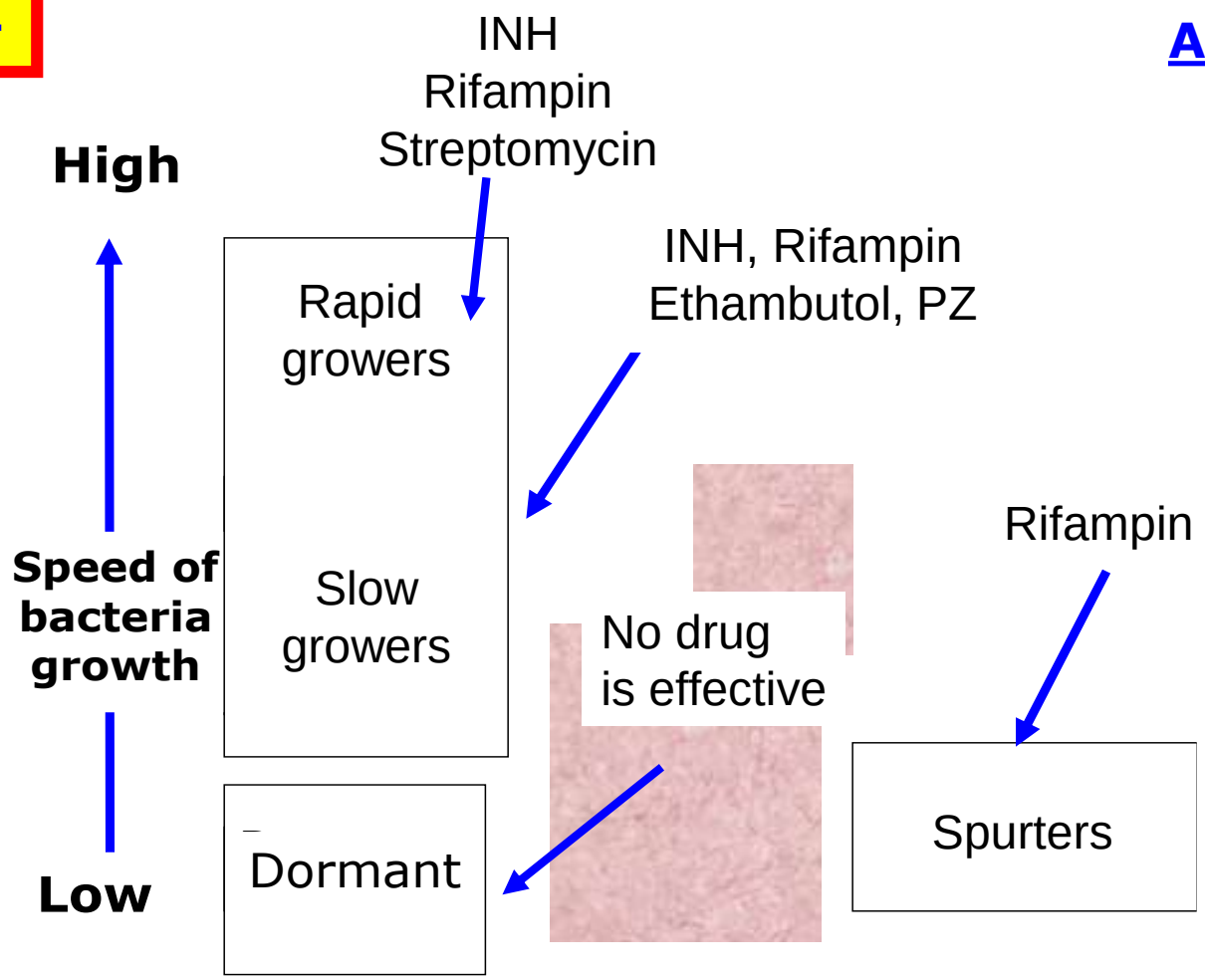
The Basis for Multi-Drug Therapy

1

- **Prevent emergence of resistance**

The Basis for Multi-Drug Therapy

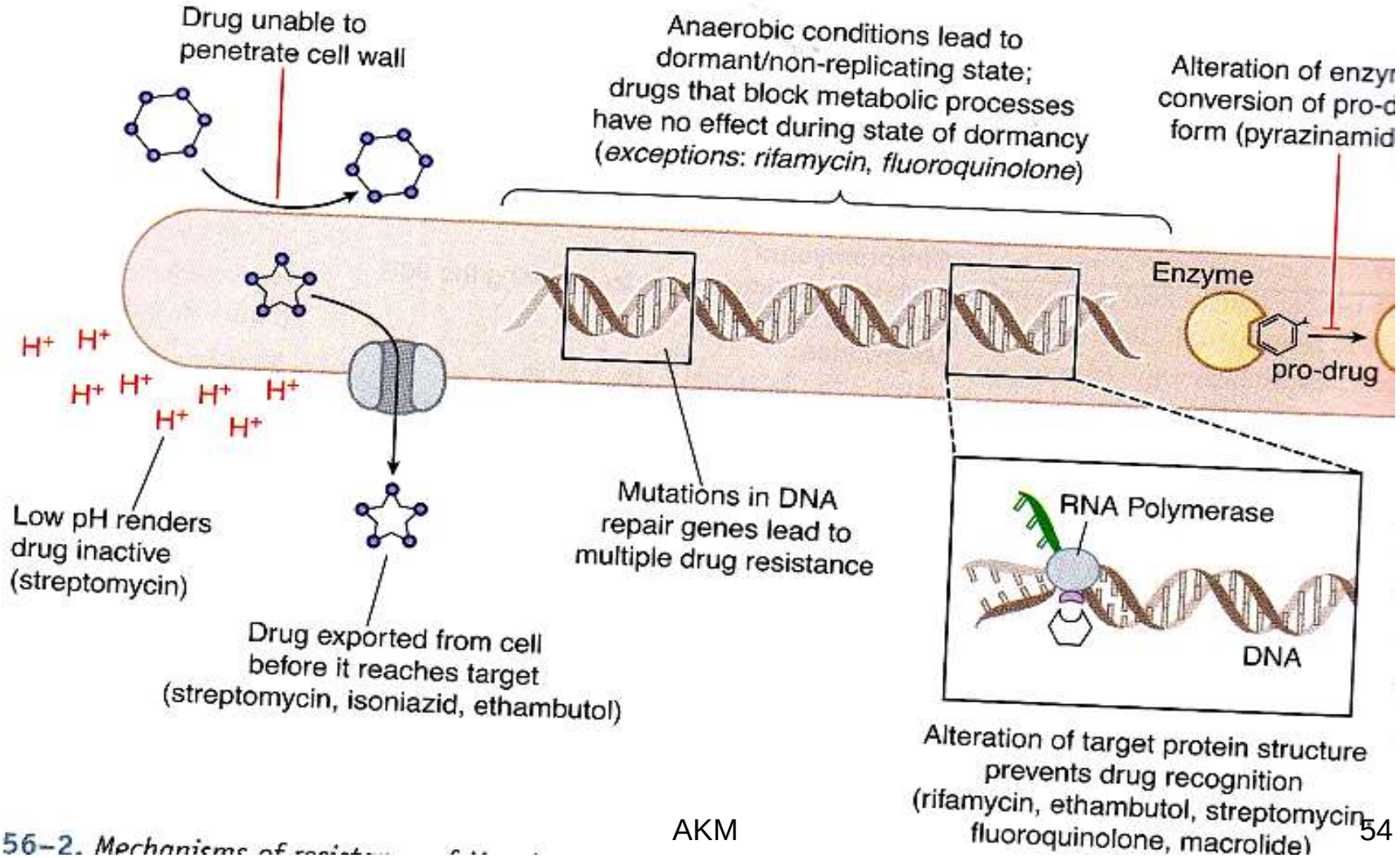
2



Antibacterial attack against all subpopulations of bacilli.

Mitchison, Tubercle 66: 219-226, 1985

Mechanism of Resistance



56–2. *Mechanisms of resist*

Relative activity of first line Drugs

- ***INH:*** potent bactericidal
- ***Rifampin:*** potent bactericidal

} **Combination is synergistic**

- ***Pyrazinamide:*** Weak bactericidal, active against intracellular bacilli.
- ***Ethamutol***: bacterisostatic, prevents resistance development.
- ***Streptomycin***: bactericidal, active against extracellular rapid growers.

Never use a single drug for chemotherapy in tuberculosis, a combination of two or more drugs must be used.

Antitubercular Agents

PAS – Paraaminosalicylic acid:

-Related to sulfonamides chemically as well as in mech. of action.

-Tuberculostatic , not add to therapeutic value , only delay resistance

-Interfere with absorption of Rifampicin

S/E - Acceptability is poor due to frequent anorexia , nausea & epigastric pain

Antitubercular Agents

Other use- Goitre

Liver dysfunction

& Blood dyscrasias

Dose- 10- 12 gm (200 mg/ kg) / day

Rarely used now

Antitubercular Agents

Ethionamide :

-Tuberculostatic , having moderate efficacy

-Acts both on extra as well as intracellular bacterias

(**Mycobacterial EthaA, an NADPH specific FAD- containing mono- oxygenases converts Ethionamide to a sulfoxide, it ↓ mycobacterial growth by ↓ the activity of the inh A gene product, the enoyl acyl reductase of fatty acid synthase II ,the same enzyme which is ↓ by INH**)

-Resistance develop readily & some cross resistance to TZN

-Absorbed orally ,distributed all over including CSF

Antitubercular Agents

S/E- Anorexia

Nausea & vomiting,

Rashes

Hepatitis ,

Peripheral/ Optic neuritis

Dose- 1 gm / day, but more than 0.5 gm not tolerated.

- seldom used now , only used in resistance cases .

Antitubercular Agents

Cycloserine (Cycs):

- Obtained from S. archidacces & is a chemical analogue of D- alanine
-↓ Bacterial cell wall synthesis
-Tuberculostatic & ↓ other G -ve organisms (E. coli , Chlamydia)
-Resistance develop slowly , no cross resist.

Antitubercular Agents

CNS toxicity is high , sleepiness , headache tremor , psychosis & convulsions

-Rarely used (only in resistance cases)

Dose – 250 mg BD

Kanamycin , Amikacin & Capreomycin:

Used as reserved drug in severe cases not responding to usual therapy

Antitubercular Agents

Newer drugs :

Ciprofloxacin

Ofloxacin

Levofloxacin

(all are used in TB & MAC)

Clarithromycin

Azithromycin

(used in MAC)

Rifabutin - > in MAC < in TB

Antitubercular Therapy

Goals-

1. Killing of dividing bacilli- drugs with bactericidal activity rapidly reduce the bact. load in the Pt & achieve quick sputum clearance – Pt become non con-tageous to the community

- Transmission is interrupted

Antitubercular Therapy

2. Killing of persistent bacilli for effective cure & prevention of relapse
3. Prevent emergence of resistance

(Drug combination are selected to maximize the above action together with consideration of cost & convenience)

- **H & R** are most efficacious drugs ,their combination is synergistic

Antitubercular Therapy

Duration of therapy shortened from 12 to 9 months.

Addition of **Z** for initial 2 months further reduces duration of treatment to 6 months

DOTs –Directly observed treatment short course ,was recommended by the **WHO in 1995**