CONGESTIVE HEART FAILURE

AIM

1. ↓ FLUID → DIURETICS
2. ↑ PUMPING → INOTROPICS

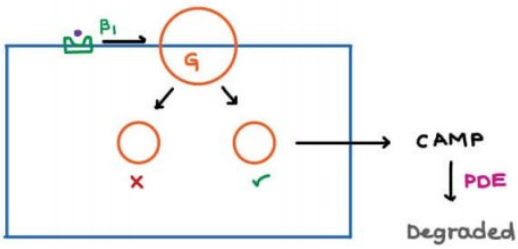
DIURETICS

LOOP DIURETICS	THIAZIDES
→ Strong	→ Weak
→ Short acting	→ Long acting
→ Used in CHF	→ Used in HTN
COMMON SIE	
→ ↓ Na^+	→ ↑ Sugar
→ ↓ K^+	→ ↑ Lipids
→ ↓ H^+	→ ↑ Uric acid
→ ↓ Mg^{2+}	
Difference	
→ Loop looses Ca^{2+} → ↓ Ca^{2+}	→ ↑ Ca^{2+}

INOTROPICS

1. β_1 AGONISTS

- DA → D_1, β_1, α_1
- DOBUTAMINE → β_1
- NA → $\alpha_1, \alpha_2, \beta_1$
- ISOPRENALINE → β_1, β_2



2. PHOSPHODIESTERASE INHIBITORS [PDEI]

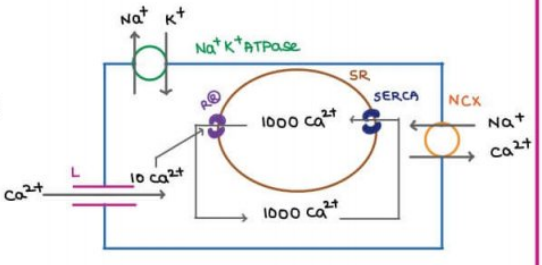
AMRINONE
MILRINONE
MA

→ also acts on Blood vessels → VASODILATION
- aka → INODILATORS

- *Inotropic DOC for right heart failure are inodilators*

3 DIGITALIS / CARDIAC GLYCOSIDES

→ Digitalis inhibits $Na^+ K^+$ ATPase
↓
NCX inhibition
↓
↑ Ca^{2+} in cytoplasm
↓
↑ Ca^{2+} in ER
↓
↑ Contractility



→ digitalis depot ↑ HR → DD ↑ in workload DD heart

→ VAGOMIMETIC EFFECT
↓
↓ HR
↓ Conduction

→ useful in ATRIAL FIBRILLATION
→ HR → 400 – 500 bpm
→ ineffective contractions → Fibrillations
→ aim of m_x → ↓ ventricular rate
Digitalis ↓ses conduction from atrium to ventricles

DIGOXIN	DIGITOXIN [Withdrawn]
→ mainly excreted by kidney C/I Renal failure	→ mainly metabolised by liver C/I in liver failure

DIGOXIN

→ only inotropic drug that can be given ORALLY
→ AE
1. Nausea, vomiting [mc]
2. Arrhythmias

mc arrhythmia	→	Ventricular bigeminy
most specific / characteristic	→	NPAT ⊂ AV Block [Non paroxysmal Atrial Tachycardia ⊂ AV Block]
not seen	→	Atrial flutter Mobitz Type II heart block

3 Gynaecomastia
4. XANTHOPSIA / YELLOW VISION

DRUGS CAUSING GYNAECOMASTIA
D, I } DIGOXIN
S → SPIRONOLACTONE
C → CIMETIDINE
O → OESTROGENS

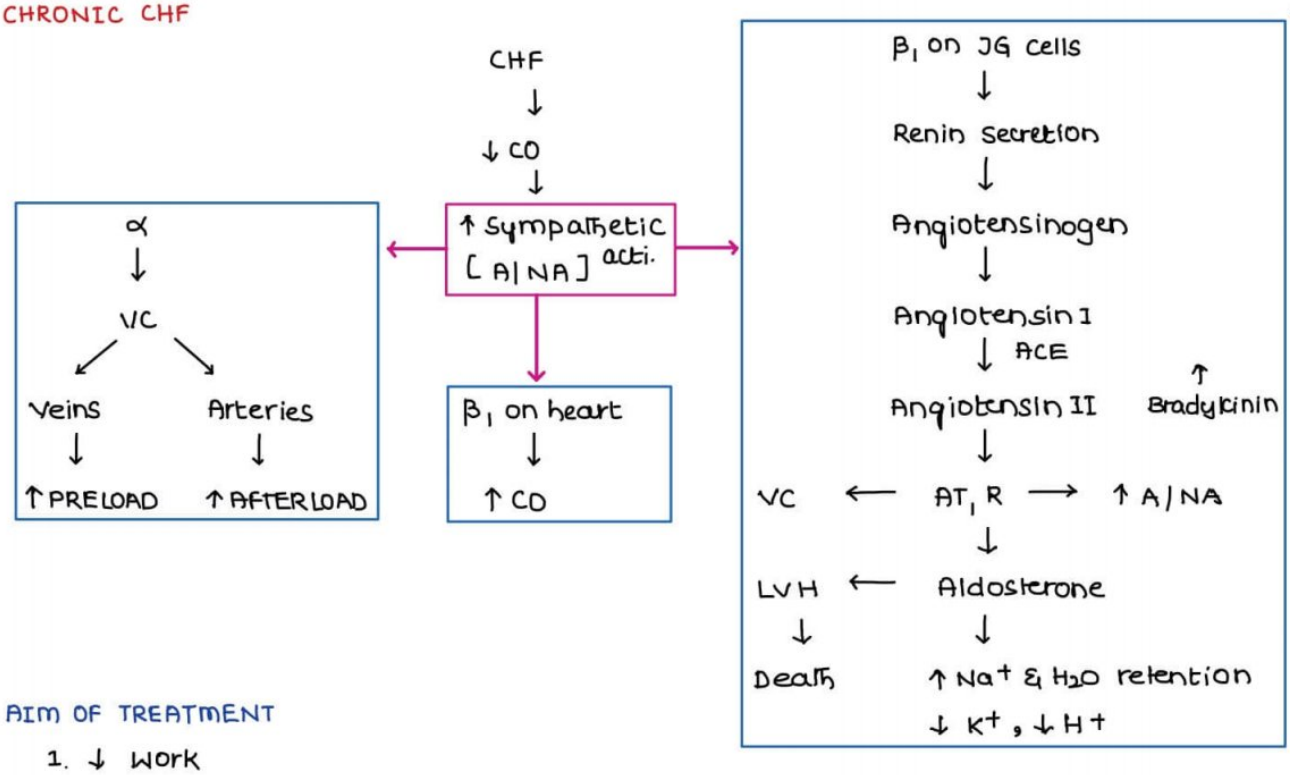
DIGITALIS TOXICITY

FACTORS ↑ing DIGITALIS TOXICITY

METABOLIC	DRUGS	PATHOLOGICAL
↑ Ca^{2+} ↓ K^+ ↓ $Mg2^+$	QUINIDINE (PK interaction; ↑ Plasma level) VERAPAMIL (PK interaction; ↑ Plasma level) AMIODARONE (PK interaction; ↑ Plasma level) THIAZIDES (PD interaction; Cause ↑ Ca^{2+}, ↓ K^+, ↓ Mg^{2+}	RENAL FAILURE: Digoxin LIVER FAILURE: Digitoxin

M_X OF DIGITALIS TOXICITY

1. correct the cause
2. DOC for Digitalis induced arrhythmias → LIGNOCAINE / PHENYTOIN
3. DIGIBIND for Severe poisoning



AIM OF TREATMENT

1. ↓ Work
2. ↓ Fluid
3. ↓ LVH [cardiac Remodelling]

1. ↓ WORK → VASODILATORS

VENO DILATORS	ARTERIO DILATORS	VENO + ARTERIO DILATORS
NITRATES	HYDRALAZINE	Na NITROPRUSSIDE ACEI ANGIOTENSIN RECEPTOR BLOCKERS

2. ↓ FLUID → LOOP DIURETICS
3. ↓ LVH [cardiac Remodelling]
   → These drugs ↓ MORTALITY
   1. β BLOCKER
   2. ACEI
   3. ANGIOTENSIN RECEPTOR BLOCKERS
   4. ALDOSTERONE ANTAGONISTS

β BLOCKERS

CARVEDILOL
METOPROLOL
BISOPROLOL

→ *Beta blockers are contra-indicated in acute CHF.*

→ *Beta blockers are used in chronic CHF and these can decrease mortality by reversing LVH*

→ *Dose of beta blocker should be gradually increased in CHF because high dose beta blocker may cause decompensation which leads to Acute Heart Failure. So, beta blockers should be started with 1/10th of final dose which is gradually increased every 2 to 3 weeks to reach the final dose in around 2 to 3 months.*

→ *Most commonly used beta blocker in CHF is carvedilol.*

ALDOSTERONE ANTAGONISTS / POTASSIUM SPARING DIURETICS

- SPIRONOLACTONE → cause gynaecomastia
- EPLERONONE -

ACEI [ACE INHIBITORS]

→ also inhibit Bradykinin metabolism [↑ Bradykinin]

→ SIE → Dry cough
Angioedema

ACL means anterior crushate ligament mnemonic

A	→	Active
C	→	captopril
L	→	Lisinopril

→ DRUGS

- → CAPTOPRIL
- → LISINOPRIL
- → ENALAPRIL → Enalaprilat
- → RAMIPRIL → Ramiprilat
- → PERINDOPRIL → Perindoprilat
- → MOEXIPRIL → Moexiprilat

} Active forms

→ ADVERSE EFFECTS

- C → Cough
- A → Angioedema
- P → Prodrugs except captopril & Lisinopril
- T → Taste alteration [Dysgusea]
- O → Orthostatic / Postural hypotensⁿ [max ↕ captopril]
- P → C/I in pregnancy
- R → C/I in B/L Renal Artery stenosis
- I → C/I in Increased K^+
- L → Lower the risk of Diabetic Nephropathy

ARBs

- T → Taste alteration [Dysgusea]
- O → Orthostatic / Postural hypotensⁿ
- P → C/I in pregnancy
- R → C/I in B/L Renal Artery stenosis
- I → C/I in Increased K^+
- L → Lower the risk of Diabetic Nephropathy

ARBs [ANGIOTENSIN [AT_1] RECEPTOR BLOCKERS]

- LOSARTAN
- VALSARTAN
- TELMISARTAN
- IRBESARTAN
- EPROSARTAN
- CANDESARTAN

S → Selective
A → AT_1
R, T } Receptor
A, N } Antagonists

→ TELMISARTAN

→ also stimulates PPAR – γ Receptor

→ Used to Reverse Insulin Resistance

LOSARTAN Lower the uric acid

→ cause ↓ in uric acid

BNP [Brain Natriuretic Peptide]

→ cause Natriuresis [↓ Na^+]

→ cause vasodilation

BNP

↓ NEP [Neprilysin] Or neutral endopeptidase

Degradatⁿ

1. NESIRITIDE
   - → Recombinant BNP
   - → not given orally, given iv
   - → Short acting
   - → Used for acute cases

2. NEP INHIBITORS

   SACUBITRIL → Effective orally

   ECADOTRIL

3. VASOPEPTIDASE INHIBITORS
   - → Inhibit both ACE & NEP
   - → OMAPATRILAT

     SAMPATRILAT

   - → S/E → cough

     Angioedema

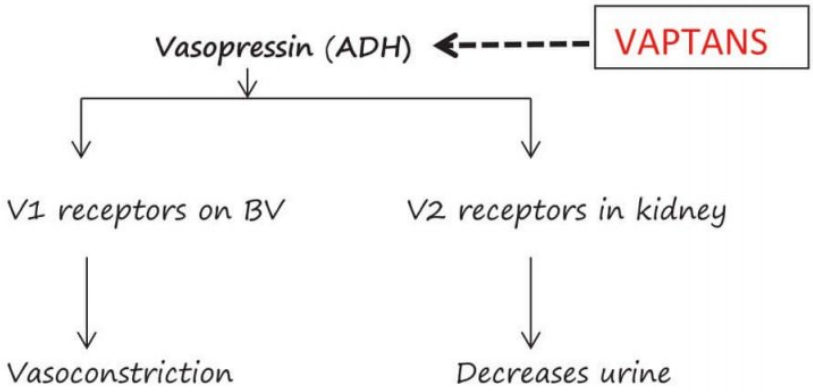
4. ARNI (ANGIOTENSIN – RECEPTOR BLOCKER + NEP INHIBITOR)

   Valsartan (ARB) + Sacubitril (NEP inhibitor)

5. FUNNY CURRENT BLOCKER

   IVABRADINE:
   - Acts by causing BRADYcardia
   - Acts by blocking funny current (I_f) in S.A node by blocking Na channels
   - S/E – ↓ in Visual Acuity

6. VASOPRESSIN ANTAGONISTS:



- In C.H.F, we need to reverse actions of vasopressin (i.e. vasodilation & ↑ urine output is required), so these receptors should be blocked → Done by Vaptans

  VAPTAN – VAsoPressin ANtagonist

CONIVAPTAN

- Given by I.V route

TOLVAPTAN

- Given orally
- Approved in APKD (autosomal dominant adult polycystic kidney disease)

ANGINA PECTORIS

I CLASSICAL / EXERTIONAL

II VARIANT
PRINZMETAL
VASOSPASTIC

CLASSICAL ANGINA PATHOLOGY

→ dlt atherosclerosis of small branches of coronary artery, Ischemia occurs

ISCHEMIA
↓
↑ Effective Diameter of artery
↓
NO pain at Ⓝ activity

→ During Exercise / Exertion, ↑ effective diameter of artery not suffice for compensation → PAIN occurs

AIM OF TREATMENT → ↓ Work on heart

VARIANT ANGINA PATHOLOGY

→ dlt SPASM OF MAIN CARONARY ARTERY
→ Pain @ rest occurs
→ Aim of TREATMENT → Dilation of coronary artery

DRUGS

I NITRATES
II CALCIUM CHANNEL BLOCKERS
III β BLOCKERS
IV POTASSIUM CHANNEL OPENERS

I NITRATES

Mechanism of action:

Nitrates
↓ Metabolized to
Nitric oxide
↓ stimulates
Guanylate cyclase enzyme
↓ which helps in formation of
↑ CGMP
↓ which activates
Protein kinase G
↓ inhibits action of
Myosin light chain kinase
↓
VASODILATION

→ Nitrates
↓ Aldehyde dehydrogenase (ALD) – more in veins > Arteries
NO
→ ALD either present in cytoplasm or in mitochondria
→ **Glyceryl Tri nitrate** is activated by mitochondrial aldehyde dehydrogenase while all other nitrates activated by cytoplasmic aldehyde dehydrogenase.
→ MOA of NO in classical angina - ↓ Preload
→ MOA of NO in variant angina – Dilation of coronary arteries

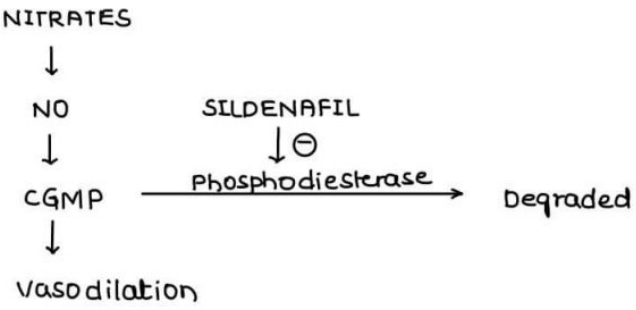
→ DRUGS

GLYCERYL TRINITRATE / NITROTRIGLYCERATE [GTN/NTG]
ISOSORBIDE DINITRATE [IDN]
ISOSORBIDE MONONITRATE [IMN]
PENTA ERYTHRYTAL TETRA NITRATE [PETN]
AMYLNITRITE [AN]

→ GTN/NTG & IDN
- → has high 1st pass metabolism
- → Sub lingual route preferred
- → DOC for acute attack of angina

→ IMN has minimum 1st pass metabolism
→ Longest acting → PETN Long name also
→ Shortest acting → AN Short name also
→ NITRATE FREE PERIOD
- → tolerance occur if nitrates continuously present
- → to avoid tolerance, 6-8 hrs of Nitrate free period should be maintained

→



NITRATES should not be given ī SILDENAFIL [Risk of Severe hypotension]

Uses of Nitrates:

A – Angina

B – Biliary colic

C – Cyanide poisoning (Drug of choice – Hydroxocobalamin)

D – Dil Ka Daura (MI)

E – Esophageal spasm

F – Failure (CHF)

Cyanide poisoning:

Mechanism:

→ Cytochrome oxidase enzyme is involved in electron transport chain to produce ATP. When it binds to cyanide during cyanide poisoning, the energy production (ATP) decreases.

→ **Hemoglobin + Amyl nitrite (Inhalational route)**

↓ forms

Methemoglobin

↓ in cyanide poisoning it forms

Cyanmethemoglobin (TOXIC METABOLITE)

↓ Sodium thiosulphate given

Sodium thiocyanate, is formed and excreted by kidney

→ Hydroxocobalamin (vit b12) if given in cyanide poisoning, it binds with cyanide to form cyanocobalamin (vit b12).

→ so one form of vitamin B 12 is converted into another form.

→ Hydroxocobalamin is the drug of choice / Antidote of choice for Cyanide poisoning which is administered in IV route.

II. CALCIUM CHANNEL BLOCKERS

→ CALCIUM CHANNELS
- → L TYPE → present in CVS
- → T TYPE → present in CNS

→ L - CALCIUM CHANNEL BLOCKERS

	BLOOD VESSELS		HEART RATE		
			DIRECT	INDIRECT	NET
VERAPAMIL	vasodilation	↓ DBP	↓↓↓	↑	↓↓
DILTIAZEM	vasodilation	↓ DBP	↓↓	↑	↓
DHP [DIHYDROPYRIDINES] NIFEDIPINE AMLODIPINE NICARDIPINE CLEVIDIPINE	vasodilation	↓ DBP	↔	↑	↑

DIHYDROPYRIDINES should be avoided in angina [↑HR]

Fast acting calcium channel blocker

→ Nifedipine
→ Clevidipine

Can cause a sudden increase in vasodilation and as a result increases HR suddenly so will not be used in angina
Can cause severe ↑↑ HR → Precipitate Angina

Therefore, these drugs are not used in Angina

Long acting drugs

→ Amlodipine and Nicardipine gradually cause vasodilation. Therefore, Tachycardia causing potential is very less. These drugs are used in Angina.

→ DOC for variant angina – CCB

→ Nimodipine – Cerebro-selective CCB

↓

Used in subarachnoid hemorrhage

→ Clinidipine – Blocks both L– Ca^{2+} # and N- Ca^{2+} channels

ADVERSE EFFECTS OF CALCIUM CHANNEL BLOCKERS

→ Headache
→ Constipation
→ Gum hypertrophy

III POTASSIUM CHANNEL OPENER

NICORANDIL

→ NO Releaser + K^+ channel opener

IV β BLOCKERS

β ⇓
↓
↓ HR
↓
↓ WORK
↓
useful in classical angina

→ β Blockers are C|I in variant angina

NEW DRUGS

I BRADYCARDIAC AGENT → IVABRADINE

Na^+ channels in SA Node
↓
Funny current [I_f]

→ Ivabradine inhibit Na^+ channel [funny current]
→ S|E → ↓ visual acuity
→ recently approved for CHF

I VA BRADI NE
I_f blocker
S|E → visual acuity
Bradicardiac agent

2. Rho KINASE INHIBITOR → FASUDIL

→ Rho Kinase → causes vasoconstriction

→ Rho Kinase ⊖ → causes vasodilation

→ FASUDIL – Used for Angina

→ NETARSUDIL – New Rho kinase inhibitor

– Approved for glaucoma treatment

3 METABOLIC MODULATORS

→ Glucose + 100 O_2 → 100 ATP [Other parts of Body]

Fatty acids + 200 O_2 → 100 ATP [Heart]

→ FA require more O_2 for same energy production

→ METABOLIC MODULATION → Making heart to utilise glucose instead of fatty acids

DRUGS

1 TRIMETAZIDINE

2 RANOLAZINE

→ also acts by blocking Na^+ channels along ↓ FA metabolism inhibition

MI

→ ANGINA → Myocardial Ischemia [Reversible]

MI → Myocardial Infarction [Irreversible]

→ NON – STEMI

Management

M → MORPHINE

O → OXYGEN

N → NITRATES

A → ASPIRIN

→ STEMI

MANAGEMENT

S → STREPTOKINASE

O → OXYGEN

N → NITRATES

A → ASPIRIN

M → MORPHINE

BLOOD PRESSURE → Lateral pressure exerted by moving column of **BLOOD** on **WALL OF BLOOD VESSEL**

ANTI HYPERTENSIVE DRUGS

1. DIURETICS
   - → ↓ BLOOD VOLUME
   - → ↓ HARDNESS OF BLOOD VESSEL [↓ S. Sodium]
2. VASODILATORS
3. SYMPATHETIC SYSTEM BLOCKERS
4. RAAS BLOCKERS

I DIURETICS

LOOP DIURETICS	THIAZIDES
→ Strong → Short acting	→ Weak → Long acting → used as 1st line drugs for HTN

II VASODILATORS

1. NO RELEASERS
   - → NA NITROPRUSSIDE
   - → HYDRALAZINE

   - → Both are Fast acting → used in HTN Emergencies
   - → Na Nitroprusside
     - → MICRODRIP SET used
       - − 64 drops → 1 ml
     - → Long term use → Leads to CYANIDE POISONING
       - → Antidote → HYDROXOCOBALAMINE
   - → HYDRALAZINE
     - → metabolised by → Acetylation
     - → SIE → SLE

Component of SHIP drugs i.e sulfonamide hydralazine isoniazid procanamide

2. L − CALCIUM CHANNEL BLOCKERS
   - → VERAPAMIL
     DILTIAZEM
     DHP
3. K^+ CHANNEL OPENERS
   - M → MINOXIDIL
   - D → DIAZOXIDE
   - H → HYDRALAZINE

DRUGS CAUSING HIRSUITSM		
P	→	PHENYTOIN
C	→	CYCLO SPORINE
M	→	MINOXIDIL

→ MINOXIDIL causes hair growth
  → used for Alopecia
  → avoided in young females

→ *MINOXIDIL is a prodrug [itself is inactive]*
- *It must be metabolized to form minoxidil sulphate [active metabolite]*
- *Activation of minoxidil is a phase II reaction.*

→ DIAZOXIDE
  → Decreases the release of Insulin
    → CI in DM
    → used in INSULINOMA

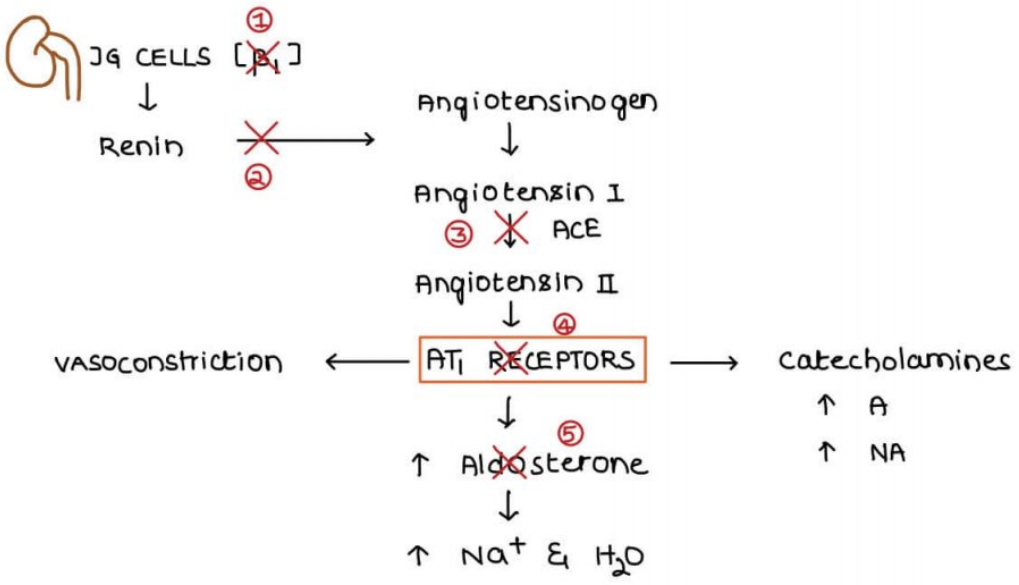
III SYMPATHETIC SYSTEM BLOCKERS

1. GANGLION BLOCKERS
→ N_N Receptor antagonists
→ TRIMETHAPHAN
  HEXAMETHONIUM
→ mainly used as Antidote for NICOTINIC POISONING

2. α_2 AGONISTS
→ CLONIDINE } Both are safe in pregnancy
  METHYLDOPA } Both can cause dry mouth & Sedation
→ CLONIDINE Sudden stoppage causes REBOUND HTN
→ METHYLDOPA can cause Hemolytic Anaemia

3. α & β BLOCKERS

IV RAAS BLOCKERS [RAAS → Renin Angiotensin Aldosterone System]



RENIN INHIBITORS

→ ALISKIREN
REMIKIREN
ENALKIREN
} ORAL DRUGS

RENIN INHIBITORS → ALISKIREN, REMIKIREN, ENALKIREN

RENIN RELEASE INHIBITORS → β BLOCKERS

TREATMENT OF HTN

JNC – 8 GUIDELINES JNC joint national committee

Category	Systolic Blood Pressure	Diastolic Blood Pressure
Normal	< 120	< 80
Pre hypertension	120 – 139	80 – 89
Hypertension (HTN)	≥ 140	≥ 90
Grade 1 HTN	140 – 159	90 – 99
Grade 2 HTN	≥ 160	≥ 100

1. BP ≥ 140/90 [any one (SBP/DBP) can be considered]
2. START Rx → BP ≥ 140/90 not controlled inspite of LIFESTYLE MODIFICATION [Low Na^+ diet & regular exercise]
3. FIRST LINE DRUGS [If there are no other compelling indications]
   - A → ACEI / ARB
   - C → CCB
   - D → DIURETICS [Thiazides]
4. GOAL
   - → < 140/90 in all patients
   - → < 150/90 in > 60 yrs patients (out DM or CKD
   - → Both SBP & DBP should be corrected
5. DOC

	JNC – 8	HARRISON
HTN in Pregnancy	→ METHYLDOPA	→ Oral LABETALOL
HTN Emergency in Pregnancy	→ HYDRALAZINE	→ IV LABETALOL
HTN	→ THIAZIDES	→ THIAZIDES
HTN Emergency	→ NITROPRUSSIDE	→ NICARDIPINE

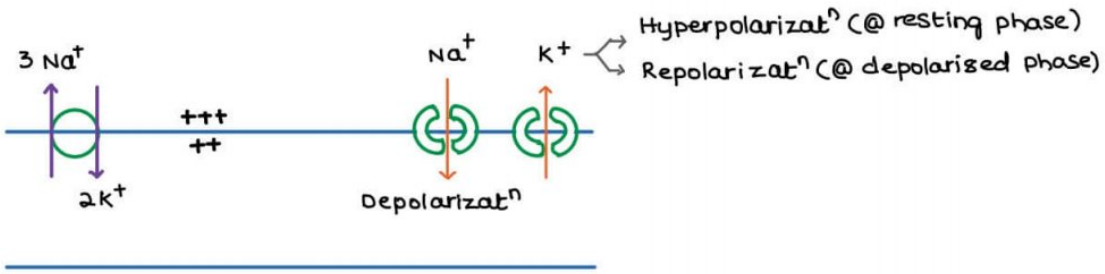
AMERICAN SOCIETY OF HYPERTENSION GUIDELINES:

Category	Systolic blood pressure	Diastolic blood pressure
Normal	<120	< 80
Elevated BP	120 – 129	< 80
HYPERTENSION (HTN)	≥130	≥ 80
HTN GRADE 1	130 – 139	80 – 89
HTN GRADE 2	≥140	≥ 90

→ Grade 1 hypertension does not require any medical treatment whereas Grade 2 hypertension requires medical treatment.

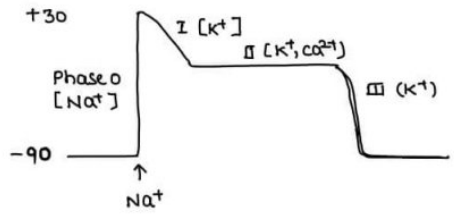
ANTI HTN DRUGS SAFE IN PREGNANCY

BETter → β # [LABETALOL]
Mother → METHYLDOPA
care → CLONIDINE
During → DHPs
HYpertensive → HYDRALAZINE
PRegnancy → PRAZOSIN [α #]



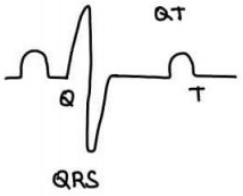
RESTING MEMBRANE POTENTIAL [−90 mV]
→ Relative negative charge inside the membrane d/t $Na^+ K^+$ ATPase
DEPOLARIZATION → d/t Na^+ entry through Na^+ channel
HYPERPOLARIZATION → d/t K^+ exit through K^+ channel at resting state
REPOLARIZATION → d/t K^+ exit through K^+ channel at depolarizatn state

ACTION POTENTIAL



1. Na^+ CHANNEL BLOCKERS
→ acts by ↓ SLOPE [dV/dt] OF Phase 0

2 K^+ CHANNEL BLOCKERS
→ ↑ Action Potential duration [APD]
→ QT INTERVAL → Depolarisatn + repolarasation
→ manifests as ↑ QT interval on ECG
→ TORSADES' DE POINTES [TDP] → ↑ QT Interval



3 K^+ CHANNEL OPENERS
→ ↓ Action Potential Duration [APD]

ANTI ARRHYTHMIC DRUGS

VAUGHAN WILLIAMS CLASSIFICATION
→ Based on predominant mechanism of action

CLASS I → Na^+ CHANNEL BLOCKERS
CLASS II → β BLOCKERS
CLASS III → K^+ CHANNEL BLOCKERS
CLASS IV → Ca^{2+} CHANNEL BLOCKERS
CLASS V → OTHERS

CLASS I → Na^+ CHANNEL BLOCKERS

→ ↓ Slope of phase 0

→ I_a → block K^+ channels → Precipitates TDP

I_b → Open K^+ channels

I_c → no effect on K^+ channels

Class Ia drugs	Class IIb drugs	Class IIIC drugs
→ Quinidine → Procainamide	→ Lignocaine → Phenytoin → Tocainide	→ Encainide → Flecainide → Propafenone
→ Causes QT prolongation	→ Used only for Ventricular arrhythmia → Lignocaine is the DOC for most of the arrhythmias	Used for WPW syndrome (Treatment of choice for WPW syndrome is radiofrequency ablation of aberrant pathway

CLASS II → β BLOCKERS

→ used in Tachyarrhythmias

CLASS III → K^+ CHANNEL BLOCKERS

B → BRETYLIUM

I → IBUTILIDE

N

D → DOFETILIDE

A → AMIODARONE

S → SOTALOL

→ SOTALOL has both CLASS III [major] & CLASS II Actions

For pulmonary fibrosis we have drugs such as cyclophosphamide(cycle) busalfan(bus) methotrexate(truck) amiodarone (drone camera) bleomycin(blew the horn)

AMIODARONE

→ Longest acting [$t_{1/2}$ → > 3wks] antiarrhythmic drug

→ MOA

1. Na^+ channel Blocker
2. β blocker
3. K^+ channel Blocker [main action]
4. Ca^{2+} channel Blocker

Dronedarone is same as amiodarone but it is less effective and doesn't cause thyroid problems

→ Indicated in all arrhythmias except TDP

→ Adverse effect of amiodarone:

- The: Thyroid(hypo/hyper) (40% iodine is present in amiodarone)
- Periphery of: peripheral neuropathy
- My: Myocardial depression
- Lung: Lung fibrosis
- Liver: Liver toxicity
- Cornea is: corneal deposits
- Photosensitive: Photosensitivity: Rash on exposure to sun (bluish: blue man syndrome)

Red man syndrome is caused by vancomycin

→ DRONEDARONE: Amiodarone without iodine but less effective and less antiadrenergic property.

→ BRETYLIUM:
- Was used for ventricular fibrillation
- Pharmacological defibrillator

→ IBUTILIDE AND DOFETILIDE:
- Used for atrial fibrillation
- Drugs like CCB, beta blockers and digoxin are also use for treatment of atrial fibrillation but these mainly control ventricular rate.
- Ibutilide and Dofetilide converts Atrial Fibrillation to normal sinus rhythm therefore it controls atrial rate also.

DRUGS CAUSING PULMONARY FIBROSIS:
- Cyclophosphamide
- Busulfan
- Methotrexate
- Amiodarone
- Bleomycin

CLASS IV → L - Ca^{2+} CHANNEL BLOCKERS

VERAPAMIL Block ca in Heart plus blood vessels

DILTIAZEM Block the ca in Heart plus blood vessels

DHPs [not used] Block ca in only blood vessels

→ used in Tachyarrhythmias

Should not combine ī β blocker [Risk of severe cardiac depression]

CLASS V → OTHERS

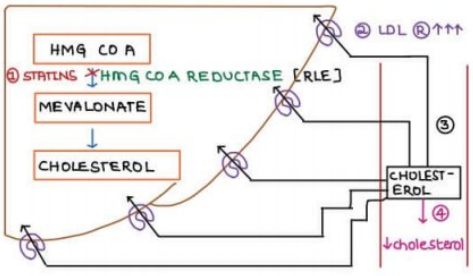
- DIGOXIN – used for AF
- ATROPINE – DOC for Bradycardia & AV block
- ADENOSINE
  - Shortest acting antiarrhythmic drug ($t_{1/2}$ < 10s)
  - DOC for PSVT
  - It is given as **Rapid IV push** in the Central veins
- MAGNESIUM – DOC for Long QT Syndrome / Torsades' De Pointes

DYSLIPIDEMIA

ANTI - DYSLIPIDEMICS

STATINS

MOA
1. Inhibit HMG - COA Reductase
2. compensatory ↑ of LDL - ®
3. Cholesterol is taken from blood
4. ↓ Serum cholesterol



Includes
- ATORVA STATIN
- ROSUVA STATIN [Longest Acting]
- PRAVASTATIN
- SIMVA STATIN
- FLUVA STATIN
- CERIVA STATIN
- PITAVASTATIN

NON ANTI DYSLIPIDEMICS ENDS ī STATIN
- CILASTATIN
- PENTOSTATIN
- SOMATOSTATIN

IMPORTANT POINTS

1. Statins have maximum LDL - cholesterol lowering potential
2. Given @ Late evening / night

   → Atorvastatin & Rosuvastatin are long acting, can be given at anytime of the day

3. ADVERSE EFFECTS
   - Myopathy → Risk further ↑'d ĩ FIBRATES
   - Hepatotoxicity
4. ↑ DM
5. PLEIOTROPIC EFFECTS [Beneficial]
   - PL → plaque stabilizatⁿ
   - E → ↓ Endothelial dysfunction
   - I → ↓ Inflammation
   - O → ↓ Oxidative stress
   - TR → ↓ Thrombosis
   - Opic

SPECIAL POINTS ABOUT INDIVIDUAL STATINS

Simvastatin and Lovastatin:

- Prodrugs
- Maximum CNS Penetration

Rosuvastatin

- Longest acting

Pravastatin

- Negligible metabolism by CYP3A4
- Risk of myopathy is very less
- Very less interaction with meals

INTESTINAL CHOLESTEROL ABSORPTION INHIBITOR [EZETIMIBE]

- Inhibit NPLICI in the intestine (so cholesterol can't be absorbed)
- There is upregulation of HMG-COA reductase on the liver, so liver will start synthesizing more cholesterol
- So ezetimide is combined with statins to Prevent tolerance

FIBRATES

→ Includes

- CLOFIBRATE
- FENOFIBRATE
- BEZAFIBRATE
- GEMFIBROZIL

→ act by PPAR α stimulation
↓
↑ LPL [Lipo protein Lipase]
↓
↓ Triglycerides

→ Fibrates have max. TG lowering potential

BILE ACID BINDING AGENTS [BABA]

→ Includes

- CHOLESTYRAMINE
- COLESTIPOL
- CHOLESEVALAM

→ MOA

ENTERO HEPATIC CYCLE → Bile Acid carry substance from gut & releases in blood & reabsorbed

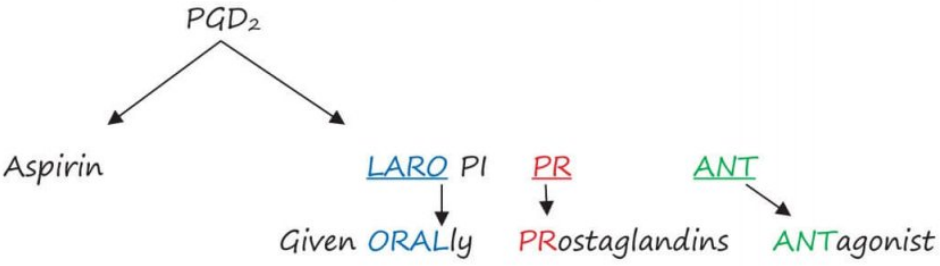
BABA interupts enterohepatic cycle & BA excreted
Liver synth s'izes BA ↑ ch l sl l > l ch l sterol

→ DOC in children & pregnancy [safe drugs]

→ Cholestyramine & colestipol not easily palatable
(Cholesevalam can be taken orally)

NIACIN [VITAMIN B_3]

- *Has MAXIMUM HDL-CHOLESTEROL INCREASING potential*
- *Only drug that DECREASES LIPOPROTEIN A*
- *Least expensive*
- *Compliance limiting adverse effects are flushing and itching (due to release of PGD_2)*
- *This can be prevented by aspirin or Laropiprant.*



- *Specifically indicated for niacin induced flushing / itching*
- *Because it will block the action of PGD_2*

- **Other side effects of niacin**
    - Hyperuricemia
    - Hepatotoxicity
    - Insulin resistance

NEW DRUGS

1. PCSK – 9 (PRE-PROTEIN CONVERTING SUBTILISIN KEXIN – TYPE 9) INHIBITORS

- PCSK-9 binds to LDL– receptors and take it to lysosomes that result in breakdown of LDL receptors.
- Thus PCSK 9 inhibitors prevent breakdown of LDL receptors. When more LDL receptors are present, they can take up more LDL-cholesterol from blood.
- So, we can use these drugs as hypolipidemic drugs.

Inhibition of PCSK – 9 formation	**Monoclonal antibody against PCSK-9**
INCLISIRAN	**ALIROCUMAB**
-Small molecule inhibitor of RNA	**EVULOCOMAB**

2. MTP (MICROSOMAL TRIGLYCERIDE TRANSPORT PROTEIN) INHIBITORS

- Triglycerides are packed in VLDL by MTP

- Drug inhibiting MTP is **LOMITAPIDE**

3. MIPOMERSEN

- Antisense oligonucleotide against Apo B_{100}
- Decrease all Apo B_{100} containing lipids

4. CETP (CHOLESTEROL ESTER TRIGLYCERIDE TRANSPORT PROTEIN) INHIBITORS

- Normally LDL cholesterol deposit in the tissues
- HDL will take up the cholesterol and bring back into the liver (reverse cholesterol transport).
- VLDL and LDL try to exchange cholesterol ester of HDL with triglyceride present in that
- This exchange is done by CETP
- Thus CETP inhibitors will increase HDL-cholesterol
- Drugs inhibiting CETP – **ANACETRAPIB**

PULMONARY HYPERTENSION

CCB [Ca^{2+} CHANNEL BLOCKER]

IV VASODILATOR TESTING

→ IF positive, DOC → CCB

→ IF negative, DOC → ENDOTHELIN ANTAGONIST

BOSENTAN

AMBRISENTAN

MACITENTAN

PDEI [PHOSPHODIESTERASE INHIBITORS] → SILDENAFIL

PGI_2 ILOPROST

PGE_2 TREPROSTINIL

→ most effective drugs for pulmonary HTN

→ can't be given orally

SELEXIPAG

→ Prostacyclin agonist

→ Can be given orally

SELE	→	Selective
XI	→	non injectable [oral]
P	→	PGI_2
AG	→	Agonist

RIOCIGUAT

→ Stimulate Guanylate cyclase → ↑ cGMP → vasodilation

-ypoa ren o — -ero

CORONARY STEAL PHENOMENON

→ *Caused by Drugs which dilate small vessels only*

→ *d/t which blood supply to ischemic area is taken towards area receiving adequate blood*

→ *Coronary steal phenomenon is also known as* ***reverse Robinhood phenomenon***

→ *Shown by*

H → *HYDRALAZINE*

I → *ISOFLURANE*

D → *DIPYRIDAMOLE*

E → *ENFLURANE*

→ ***Beta blockers*** *are found to cause* ***Robinhood phenomenon*** *as these increase the blood flow to the ischemic area as compared to non-ischemic area*

COUGH

DRY COUGH	PRODUCTIVE COUGH
Rx by ANTITUSSIVES CODEINE PHOLCODEINE DEXTROMETHORPHAN NOSCAPINE	Rx by MUCOKINETICS • Expectorants • Mucolytics

Mucokinetics (Aid in removal of secretions from lungs)

Expectorants (Increase secretions)

- Guafenesin
- Potassium iodide

Mucolytics (Lyse mucus)

- Ambroxol
- Bromhexine
- Acetylcysteine
- Dornase alfa

BRONCHIAL ASTHMA

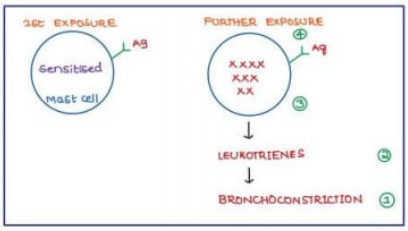
1. BRONCHODILATORS

a. SYMPATHOMIMETICS

β_2 AGONISTS

given by inhalation:

- SALBUTAMOL, TERBUTALINE — Short acting — used in acute attacks
- SALMETEROL, FORMETEROL — Long acting — used for prophylaxis



→ SALMETEROL → Slow acting → only used for Prophylaxis
FORMETEROL → Fast acting → can also be used for Acute Attacks

→ S/E of β_2 AGONISTS

- T – Tachycardia
- T – Tremors (Most common side effect)
- T – Tolerance (Mainly with long acting beta 2 agonists)
- T – T wave changes (Because of hypokalaemia)

These drugs also cause hyperglycaemia

b. PARASYMPATHOLYTICS

M_3 BLOCKERS

IPRATROPIUM
TIOTROPIUM

→ given by inhalational route
→ DOC for acute attack in patients on β blocker therapy

c. PDEI [PHOSPHODIESTERASE INHIBITORS]

- Include Theophylline and aminophylline
- Given orally or by intravenous route (not available by inhalational route)

Mechanism

→ Inhibits PDE (thereby ↑ cAMP)
→ Adenosine A_1 receptor antagonist
→ Can restore the activity of histone deacetylase (anti-inflammatory action)

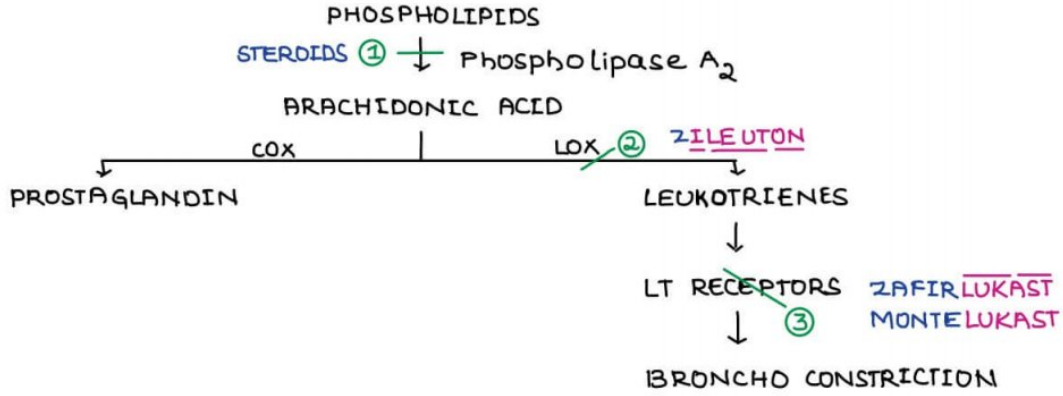
Adverse effects

Due to PDE inhibition	Due to adenosine A1 antagonism
GIT: Nausea, Vomiting, Diarhhea	Diuresis
Headache	Seizures
Arrhythmias	Arrhythmias

Special points

→ Theophylline follows zero order kinetics
→ Theophylline is metabolized by microsomal enzymes, so prone to drug interactions
  - Enzyme inducers (like smoking) decrease the effect, therefore smokers require higher doses
  - Enzyme inhibitors (like ciprofloxacin and erythromycin) can result in toxicity (seizures, arrhythmias etc.)

2.



STEROIDS
→ DOC for prophylaxis
→ also used in acute attack along ī bronchodilators

→ **Inhalational corticosteroids:**

- Beclomethasone
- Budesonide
- Fluticasone
- Flunisolide
- Triamcinolone
- Mometasone
- Ciclesonide

→ Only 5% of inhalational corticosteroid reaches the bronchus, 95% sticks on epithelium of respiratory pathway leading to immunosuppression.
- MC side effect is oropharyngeal candidiasis
- Topical Nystatin is used to treat candidiasis
- Gargling after every dose will prevent this adverse effect

→ Ciclesonide is a prodrug which is activated only in bronchus, therefore, it doesn't cause candidiasis.

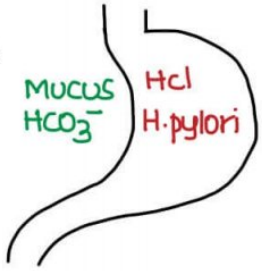
3. MAST CELL STABILIZERS
→ Include
- SODIUM CROMOGLYCATE
- NEDOCROMIL

→ Only used for prophylaxis

4. OMALIZUMAB
→ monoclonal antibody against IgE
→ Only used for prophylaxis
→ given subcutaneously

GASTROINTESTINAL TRACT

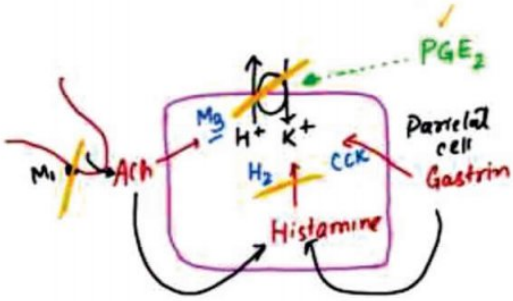
PEPTIC ULCER DISEASE
→ dlt imbalance between Aggressive & protective factors
- Aggressive factors → HCl , H. pylori
- Protective factors → mucus & HCO_3^-



TREATMENT
1. ↓ ACID

HCl
→ produced by Parietal cell of Stomach
→ PROTON PUMP [H^+K^+ PUMP]
→ helps in Secretn of Acid
→ stimulated by
- Ach [M_1]
- Histamine [H_2]
- Gastrin [CCK]

→ inhibited by PGE_2



MYCOBACTERIAL DISEASES

TUBERCULOSIS

ANTI TUBERCULAR DRUGS

FIRST LINE DRUGS

- H → ISONIAZID
- R → RIFAMPICIN [RCIN]
- Z → PYRAZINAMIDE
- E → ETHAMBUTOL
- S → STREPTOMYCIN

	ACTIVITY	BACTERIA	HEPATOTOXIC	PREGNANCY
H	cidal	Both	✓	Safe
R	cidal	Both	✓	Safe
Z	cidal	i/c	✓✓✓	avoided
E	static	Both	×	Safe
S	cidal	e/c	×	C11

MYCOBACTERIA	LOCATION	MOST EFFECTIVE DRUG
FAST GROWING	Wall	H
INTERMEDIATE GROWING	Spurters [casseous necrosis]	R
SLOW GROWING	i/c	Z

ISONIAZID (INH)

- Causes pyridoxine (vitamin B6) deficiency resulting in peripheral neuropathy. So, pyridoxine is used for treatment as well as prevention.
- Hepatotoxic (INH: Isoniazid causes Neuropathy and Hepatotoxicity)
- Metabolized by acetylation and cause SLE as an adverse effect (SHIP).
  - →Isoniazid is metabolized by N – Acetyltransferase to form acetyl isoniazid and it is further metabolized to form acetyl hydrazine
  - →Isoniazid accumulation can cause
    - Peripheral neuropathy
  - →Acetyl hydrazine can cause
    - Hepatotoxicity
  - →In slow acetylators, there is less amount of N – Acetyltransferase leading to slow metabolism leading to isoniazid accumulation causing peripheral neuropathy
  - →In fast acetylators, there is more amount of N – Acetyltransferase leading to acetyl hydrazine accumulation causing Hepatotoxicity.

SHIP drugs:
S – Sulfonamides
H – Hydralazine
I – Isoniazid
P – Procainamide

RCIN

1. Should given on empty stomach
2. Secreted in Bile → safe in RF
3. Enzyme Inducer

INTERACTIONS

Warfarin — Replace t → Heparin

OCP — Replace t → other contraceptive method

Anti HIV drugs → RCIN replaced t RIFABUTIN

	RIFABUTIN	RIFAMPICIN
Enzyme inducer	+	+ + + +
Durat^{n} of act^{n}	Longer acting	Long acting
Effective on	Atypical mycobacteria	M.TB
S/E	no hepatotoxic Pseudojaundice Uveitis	Hepatotoxic

4. *Causes discoloration of secretions:*

→ *Orange colored urine*

→ *Staining of contact lens due to discoloration of tears*

5. *OTHER USES:*

→ *Leprosy*

→ *DOC for Brucella (doxycycline + rifampicin)*

→ *Effective against Gram positive bacteria (including MRSA)*

→ *Effective against Gram negative bacteria (including Pseudomonas)*

→ *It was used for prophylaxis of meningococcus meningitis*

Meningococcal meningitis prophylaxis
Ciprofloxacin (DOC)
Ceftriaxone (most effective drug; Injectable: DOC in pregnancy and children)
Rcin (Not preferred now)

PYRAZINAMIDE (Z)

→ *Effective only against intracellular bacteria*

→ *Most hepatotoxic*

→ *Causes hyperuricemia*

→ *Possess the best sterilizing activity (can kill the slow growing bacteria) and makes the medium sterile.*

ETHAMBUTOL (E)

→ Affect eye

- Red green colour blindness (optic neuritis)
- Initially reversible, later irreversible
- Avoid in <64 year age children

STREPTOMYCIN (S)

→ Not effective orally (given i.m.)

→ Nephrotoxic

→ Ototoxic

→ Cause neuro-muscular blockade

→ Streptomycin was initially in first line anti tubercular drugs, it was shifted to supplementary category as it needs to be given as injection. Now-a-days it is not even considered as first line drug.

2ND LINE DRUGS

1. FQ
   - → OFLOXACIN
   - → MOXIFLOXACIN
   - → GATIFLOXACIN
   - → LEVOFLOXACIN
2. INJECTABLE
   - → CAPREOMYCIN
   - → KANAMYCIN
   - → AMIKACIN
3. LINEZOLIDE – Also used for VRSA
   CLOFAZIMINE – Also used for multibacillary leprosy
4. CYCLOSERINE – Causes neuropsychiatric S/E
   ETHIONAMIDE – Hepatotoxic, causes hypothyroidism
   PAS – Causes hypothyroidism
5. OTHER DRUGS

- Thioacetazone:
  - Never given in HIV patients
- Antitubercular with uncertain efficacy:
  - Amoxycillin + clavulanic acid
  - Imipenem
- New drugs approved for MDR/XDR TB:
  - BEDAQUILINE act by inhibiting ATP synthase enzyme, can result in QT prolongation

- **DELAMANID** act by inhibiting mycolic acid in mycobacteria, can result in QT prolongation
- **PRETOMANID** act by inhibiting mycolic acid in mycobacteria, is hepatotoxic

- **NEW REGIME FOR MDR / XDR TB: BPaL REGIME:**
  - Bedaquiline (B)
  - Pretomanid (Pa)
  - Linezolid (L)

TREATMENT OF TUBERCULOSIS (RNTCP 2018):

- **DRUG SENSITIVE TB:**

Drug sensitive	IP	CP
Category 1	2 HRZE	4 HRE
Category 2	2 HRZE	4 HRE

- **DRUG RESISTANT TB:**

Mono drug	Resistant to any one of HZE
Poly drug	Resistant to more than one of HZE
Multi drug (MDR)	Resistant to H+R
Rifampicin resistance	Resistant to R but sensitive to H
Extensive (XDR)	Resistant to H + R + one of FQ + one of injectable
Total (TDR)	Resistant to all available drugs for TB

- **Treatment**
  - Drug sensitivity testing is done before we start antitubercular drugs for MDR, RR and XDR.

Resistant TB	IP in months	CP in months
Mono	3 (FLD + Lf + Inj)	6 (FLD + Lf)
Poly	3 (FLD + Lf + Inj + Ethio)	6 (FLD + Lf + Inj + Ethio)
MDR	6 (minimum 6 drugs)	18 (minimum 4 drugs)
RR	6 (Tx of MDR + H)	18 (Tx of MDR + H)
XDR	6 (minimum 7 drugs)	18 (minimum 6 drugs)

FLD: First line oral drugs to which bacteria is sensitive

Lf: levofloxacin

Inj: injectable drug

Ethio: Ethionamide