THERAPEUTICS NOTES
LEVEL VI MBCHB
2019

COMPILED BY NAILA KAMADI

1. PRINCIPLES OF THERAPEUTICS LEVEL VI MBCHB 2019

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OUTLINE

- Pharmacodynamic & pharmacokinetic changes in renal & liver diseases
- Pharmacogenetics
- Gene – based therapy
- Drug Interactions
- Adverse Drug Reactions
- Immunopharmacology
- Principles of prescription writing

PHARMACODYNAMIC & PHARMACOKINETIC CHANGES IN RENAL & LIVER DISEASES

BY: DR. INDALO

Renal impairment

- **Kidney is not functioning as well as other people's of the same age gp**
- **All the 3 processes (filtration, active transport & reabsorption) may be affected**
- **Renal patients treated with a variety of drugs, both for their disease and intercurrent illness**
- **Drugs eliminated primarily by renal excretion may accumulate unless the dosage regimen is adjusted**
- **Therapy further complicated by changes in protein binding, drug distn, irregular GIT absorption, potential effects on drug metabolism and dialysis Txs**

Effect of renal impairment on P'kinetics

ABSORPTION:

- **Unpredictable in uraemia as nausea and vomiting are frequently present**
- **Alteration of absorption**

DISTRIBUTION:

- **Albumin commonly passed in urine in renal disease → Hypoalbuminaemia causes an increased [] of the unbound drug in plasma & reduced drug protein binding e.g. dose of phenytoin higher in normal individuals but lower doses in renal impairement ~ free [drug] required to produce antiepileptic effect**

- Plasma protein binding can be reduced despite albumin levels being in the normal range ~ endogenous binding inhibitors e.g. H^+ which are retained in renal failure & bind to receptors for acidic drugs such as s/amides, penicillin & salicylates, enhancing their potential to cause toxicity
- Anomalies in Vd in patients with oedema

- **Salt and water overload/depletion may occur in those with renal disease affecting [D] obtained from a given dose**
- **Effect of renal disease on the elimination of a drug depends on the renal status of the patient & the elimination characteristics of the drug**

METABOLISM:

- Oxidative metabolism by the liver may be altered in uraemia ~ rarely of clinical significance
- Reported that there is regeneration of parent drugs from glucuronide conjugates of such drugs as lorazepam, diflusinol & clofibrate when their conjugates accumulate in renal failure
- Drug metabolites can accumulate & exert P'cologic effects, inhibit metabolism of their parent cpd or displace it from protein binding & cause toxic effects

- **Insulin is in part catabolised by the normal kidney but this is reduced in renal disease – insulin reqs of diabetics decline as RF deteriorates**
- **1-hydroxylase (located in the kidney) production declines & so conversion of 25-hydroxycholecalciferol (calcifediol) to the more active metabolite 1,25-dihydroxycholecalciferol (calcifetriol) is reduced ~ osteodystrophy seen in renal failure**

RENAL ELIMINATION:

- Reduced elimination of drugs normally excreted by the kidneys e.g. gentamicin; metabolites of lipid-soluble drugs may themselves be water soluble & potentially toxic

END ORGAN SENSITIVITY:

- Response to drug Tx may be reduced in renal disease e.g. mild thiazide diuretics have little diuretic effect in patients with severe renal impairment

Alterations in drug receptors

- **Uraemic patients have increased tendency to experience undesirerable SEs of certain drugs causing the level of tolerance to be lower than in normal patients.**
- **Effect probably involves morphological modification of the drug receptors or interactions with substances retained in renal insufficiency**
- **e.g. dose of thiopentone necessary to induce sleep is about half of the one used in subjects with normal blood urea. Similar results may occur with other psychoactive drugs**
- **Hypersensitivity of the nervous tissue to drugs in cases of uraemia could be due to menengeal & cerebral permeability which is often increased in renal insufficiency**

- Increased sensitivity to the toxic effects of antibiotics e.g. moderate doses of colistin and plasma levels in the therapeutic range may cause neuropsychiatric symptoms starting 30-60 mins after the 1st injection
- Other humoral disturbances affect sensitivity, notably acidosis e.g. increases passive tubular reabsorption of barbs; favours the penetration of some drugs into the cell; slows down the metabolic degradation of curare-like drugs contributing to problems of recurarisation

- **Small doses of drugs safe under normal conditions may cause severe or even fatal side effects**
- **Risk of retention concerns those drugs mainly excreted by the kidneys**
- **Impaired RF affects the renal exrn of some drugs, their protein binding and Vd, & in some cases metabolism of the drug**

- **Dose correction in renal impairment should be based on total body CL (kV) since in impaired RF, k_e, k_{nr} & Vd may all be changing with some drugs rather than just k_e**
- **T half of some drugs change sufficiently in renal impairment to warrant change in the usual dose regimen to prevent accumulation to toxic levels**

- To adjust dose the KF must be established ~ use CL_{creat} or CL_{inulin}
- KF value of the renal patient is used in calculating drug dose for the patient.
- Normograms can also be used to estimate dosage regimens in patients with kidney disease.
- Dose adjustment may involve ↑ in τ/↓ dosage or both.
- NB: immediate therapeutic efficacy is important → LD is essentially unaltered for patients with renal impairment

  NB: Use of serum levels will avoid serious over- or underdosage e.g. with anticonvulsants, cardiac gylcosides, antibiotics, antiarrhythmics & psychotherapeutic drugs

- **Closely monitor all patients with renal disease particularly for signs of unexpected drug toxicity**
- **Select within a given therapeutic gp of drugs, a cpd that is particularly safe and easy to use & if possible does not require adjustment of dosage – this is the drug of choice for renal patients. Such drug would meet the following P'kinetic criteria:-**

  → Normal urinary excrn less than 30% of the administered dose

  →Predorminant billiary & intestinal removal

→Disposition essentially unaffected by parameters likely to be modified in renal failure e.g. changes in serum protein or fluid compartments, receptor sensitivity etc and →P'kinetics not complicated by the formation of active metabolites that depend on urinary excretion (elimination) and above all

→ The drug should have a wide therapeutic margin and must be free of nephrotoxicity

NB: in patients requiring dialysis, adjust for drug removal by the artificial membrane ~ small molecules unbound to proteins are most easily removed

DRUGS AND THE LIVER

- **Major site of drug biotransformation**
- **Drugs converted from fat soluble to water soluble substances that can be excreted in the urine**
- **Liver disease can affect drug absorption, hepatic metabolism, tissue distribution and protein binding**

- **Patients with liver disease are susceptible to a number of complications e.g. ascitis, varices , encephalopathy – the risk of these occurring are dependent on the nature and severity of the disease**
- **The side effects of drugs can exacerbate these complications, increasing the risk & worsening the patient's condition**
- **Effect on P'kinetics of the drugs is unpredictable but elimination of many potent drugs is impaired in patients with chronic liver disease**

- **Unpredictability relates to the multiple effects that liver disease produces ~ effects on drug metabolizing enzymes, on drug binding and on hepatic blood flow; complexity of the hepatic metabolism of drugs; some enzymes are far more sensitive to the effect of disease than others**
- **Antipyrene has negligible plasma protein and tissue binding, & is eliminated exclusively by hepatic metabolism with a low intrinsic CL . Its T half and CL are considered sensitive indicators of LF wrt oxidative metabolism processes**

- In cirrhosis glucuronidation is spared relative to oxidative drug metbsm
- In advanced cirrhosis glucuronidation may also be substantially impaired; other conj pathways impaired to various degrees
- Liver synthesizes (proteins) albumin, enzymes etc. In liver disease there is impaired protein binding probably due to reduced [albumin]; accumulation of endogenous biochemicals e.g. bilirubin also occurs and may be a contributory factor

Hepatic CL of drugs in cirrhosis

Affects drug disposition in 2 ways:

→First pass effect less than in normal liver ~ ↑ F of drugs that undergo 1st pass metabolism

→Reduces hepatic perfusion & enzyme activity ~ lower hepatic CL of drugs with high intrinsic hepatic CL from the blood stream e.g. increased F of β-blockers such as metoprolol

- **LFTs & parameters of drug elimination can be done but don't reflect <u>quantitative</u> ability of the liver to metabolize drugs**

- **Drugs with low hepatic E & are largely cleared by metabolism in the liver are rate limited by the activity of hepatic drug metabolising enzymes ~ CL sensitive to changes in hepatic enzymes 2ry to disease**
- **A given liver disease does not affect CL of all drugs to the same extent e.g warfarin, salicylate & phenytoin unimpaired by certain liver diseases**

- **In patients with liver disease dosage should be kept low for drugs metabolized by the liver ~ preferably give drugs cleared by the kidneys**

- Evidence that with moderate degree of hepatic impairment there is a decrease in CL of drugs or active metabolites normally cleared by the kidneys
- The effect of renal CL of unbound drug may be masked if there is concomitant decrease in plasma protein binding of the drug
- Serum creat and CLcreat not useful markers of renal dysfunction associated with cirrhosis ~ may over estimate RF due to increased fractional renal tubular secretion of creat

Effect of liver disease on P’dynamics

- **Patients with cirrhosis may also experience altered sensitivity to the pharmacological actions of drugs, particularly enhanced CNS effects, enhanced renal SEs with NSAIDS, and reduced sensitivity to some diuretics**

- **Different types of liver disease can affect drug kinetics in different ways therefore difficult to give general advice.**
- **If clinical study for a particular drug is available - give advice on dose adjustment**
- **If no clinical studies - use information from healthy individuals to try & predict the effect the patient's liver disease may have on drug handling**
- **The following P'kinetic parameters for the drug in Q may be affected by the liver disease and there may be need for dose adjustment:-**

- **Solubility of oral form – lipid or water soluble (may affect extent of absn & distn)**
- **F- may help identify drugs with high 1st pass metsm**
- **Distribution – into ascitis?**
- **Protein binding – high or low?**
- **Metabolism – hepatic or other type; prodrug; active or inactive met; high fast pass met or E**
- **Excretion – renal or billiary, enterohepatic recycling?**
- **Half life**

- **As well as taking P’kinetic & P’dynamic changes into account, important to also consider the SE profile of the drug and the patient specific factors such as age, co-morbidities etc**

- **Determination of drug dosage in cirrhosis requires information on changes in P'dynamics, plasma prot binding in addition to changes in drug elimination**
- **In a variety of liver diseases without cirrhosis (e.g. carcinoma, schistosomiasis and viral hepatitis), impairment of drug elimination may not be sufficient to warrant reduction of drug dosage**
- **If cirrhosis present → possibility of multiple interactions between changes in hepatic and renal disposition & P'dynamics**
- **In chronic liver disease with cirrhosis, reduce dose regardless of the route of elimination of the metabolite**

PHARMACOGENETICS
27/5/2019

BY: DR. MUASYA

TYPED BY NAILA KAMADI

Introduction

- **Pharmacogenetics** is the study of genetic influences on responses to drugs.
- **Genes** are the fundamental units of heredity. They consist of ordered sequence of nucleotides (***adenine, guanine, thymidine cytosine***) located in particular positions in a particular DNA strand.
- **Pharmacogenomics** is the study of the use of genetic information to guide the choice of drug therapy on an individual basis.
  - It employs tools for surveying the entire genome to assess multi – genic determinants of drug response.

Cont.

- Individuals differ from each other in ~ every 300 to 1000 nucleotides.
- Genetic variation can be inherited through **germline** or **acquired mutations** e.g. somatic mutation in a tumor
- Genetic variations can be:
  1. Single Nucleotide Polymorphisms (SNPs) i.e. single base pair substitutions in the genome (occur at frequencies in ≥ 1% in a population)
  2. Insertions/ deletions (***indels***)
  3. Copy number variants OR
  4. Short tandem repeats

Cont.

- **Alleles** one of ≥ 2 alternative forms of a gene that arise by mutation & are found at the same place on a chromosome.
- **Genotyping** is the determining the combination of alleles (variants) at a specific location in the genome.
- **Genetic variation** are the differences in genetic sequences among individuals in a population.

Factors which determine inter – individual variability in response to drugs

- Drug – drug interaction: *can be beneficial or harmful*
- Drug – food interactions e.g. grapefruit juice
- Age, sex, pregnancy
- Disease states
- Genetic factors

Pharmacogenetic phenotypes

- Candidate genes for therapeutic & adverse response can be divided into 3 categories:
  1. ***Pharmacokinetic***: Those which modify drug disposition.
  2. ***Pharmacodynamic (receptor – target)***: Alter the function of the molecules with which drugs interact to produce their beneficial or adverse effects.
  3. ***Disease modifying***: Those that alter the broad biologic environment in which the drugs interact with target molecules, including the changes associated with the diseases for which the drugs is being prescribed.

1. Pharmacokinetic alterations

- Pharmacokinetic germline variability in genes that encode determinants of the PK of a drug.
- The pharmacokinetic variables involve
  1. Metabolizing enzymes
  2. Transporters
- Types of PK alterations:
  a. Single gene disorders inherited in Mendelian fashion
  b. Alteration of phase I drug metabolism
  c. Alteration of phase II drug metabolism

a. Single gene disorders inherited in Mendelian fashion

Plasma cholinesterase deficiency

- Succinylcholine sensitivity is due to genetic variation in the rate of drug metabolism as a result of a Mendelian autosomal recessive (AR) trait.
- This short acting NMBD is widely used in anesthesia. It is rapidly hydrolyzed by ***plasma cholinesterase.***
- 1 in 3000 individuals fail to inactivate succinylcholine rapidly & experience prolonged neuromuscular block if treated with it.

Cont.

- It is because of a recessive gene that gives rise to an abnormal type of plasma cholinesterase. The abnormal enzyme can be detected using the ***dibucaine number***
- Only homozygotes express the disease:
  - They appear completely healthy unless exposed to succinylcholine or closely related chemicals. However they experience prolonged paralysis if exposed to a dose that would cause NMB for only a few minutes in a healthy person.
- Response to succinylcholine may also be abnormal in patients due to ***malignant hyperthermia*** (this is a genetically determined idiosyncratic adverse drug reaction involving the ryanodine receptor)

b. Alteration of phase I metabolism

- ***Polymorphism***: variation in DNA sequence that is present at an allele frequency of ≥1% in the population
- There are ~10M SNPs.
- They have ethnic & geographical variability

Effect of genetic polymorphism

- Increased effective dose
- Extended pharmacological effect
- ADRs
- Lack of prodrug activation
- Exacerbation of drug – drug interaction
- Drug toxicity
- Metabolism through alternate pathways

There are 3 CYP genetic polymorphisms that have been well characterized

1. CYP2D6 polymorphism
2. CYP2C9 polymorphism
3. CYP2C19 polymorphism

CYP2D6 polymorphisms

- There are > 50 polymorphic variants
- The function of this enzyme is inherited in an AR manner
- The many genotypic variants yield 4 main phenotypes of CYP2D6
  1. Poor metabolizers (PM) who have deficient enzyme
  2. Intermediate metabolizers (IM)
  3. Extensive metabolizers (EM)
  4. Ultra rapid metabolizers (UM): have multiple copies of the CYP2D6 gene (duplication 2D6); They require higher doses of CYP2D6 drug substrates for efficacy

Several drugs are metabolized by CYP2D6 including:

- Opioids e.g. pethidine, codeine, morphine, dextromethorphan
- Beta blockers e.g. metoprolol, propranolol
- SSRIs e.g. fluoxetine
- Antipsychotics e.g. haloperidol

Hydroxylation polymorphisms in CYP2D6 explains an increased susceptibility to severe ADRs e.g.

- ***Nortriptyline***: headache and confusion in PM.
- ***Codeine***: weak (or non – existent) analgesia in PM who convert less codeine to morphine.
- ***Phenformin***: excessive incidence of lactic acidosis in PM.

CYP2C9 (tolbutamide polymorphism)

- 6 polymorphic variants have been identified
- CYP2C9 polymorphisms cause reduced enzyme activity leading to slow metabolizers.
- Drugs metabolized by CYP2C9 are eliminated slowly in poor metabolizers & these patients are susceptible to dose related ADRs
- Such drugs include:
  - S – warfarin, losartan, celecoxib & the sulphonylureas e.g. tolbutamide

CYP2C19

- CYP219 polymorphisms cause reduced enzyme activity leading to poor metabolizers.
- Require lower doses of drugs metabolized by the enzyme e.g.
  - PPIs
  - Some anticonvulsants

d. Alteration of phase II metabolism

- Include:
  - Acetylation
  - Sulphation

Acetylation (N – acetyl transferase)

- INH is metabolized in the liver by acetylation.
- Administration of identical doses (per kg) of isoniazid → variability in blood concentrations.
- There is a bimodal distribution of fast & slow acetylators.
- Inheritance is via a Mendelian fashion: Heterozygotes as well as homozygotes are rapid acetylators as rapid metabolism is inherited via AD.

Cont.

- Slow acetylators:
  - INH toxicity in the form of ***peripheral neuropathy*** most commonly occurs in slow acetylators.
  - Slow acetylators are also more likely to show phenytoin toxicity because INH inhibits hepatic microsomal hydroxylation of phenytoin.
- Rapid acetylators:
  - Slower response to INH & higher risk of relapse of TB infection are more frequent in rapid acetylators.
  - Isoniazid hepatitis may be more common in rapid acetylators.

Cont.

- Acetylators status affects ***procainamide*** and ***hydralazine***
- ~ 40% of patients treated with procainamide for > 6months develop ANA.
  - Slow acetylators are more likely to develop ANA & more slow acetylators develop procainamide induced SLE.
- Similarly, lower doses of hydralazine are required to control HTN in slow acetylators. Slow acetylators are more susceptible to hydralazine induced SLE.

Sulphation

- Sulphation by sulfotransferase (SULT) enzymes shows polymorphism.
- SULT enzymes metabolize ***estrogens***, ***progesterone*** and ***catecholamines***
- The polymorphic forms have reduced activity

2. Genetic influences on drug action

- There are many variant in receptors e.g. ***ER, β adrenoceptors, dopamine (D2) receptors & opioid μ receptors***
- Such variants produced altered receptor expression/ activity:
  - The β_2 adrenoceptor polymorphism (SNPs yield a reduce response to salbutamol with increased desensitization)
  - Variants in platelet glycoprotein IIb/ IIIa receptors modified the effects of eptifibatide
  - Genetic variation in serotonin receptors influences the effects of antidepressants such as fluoxetine and clomipramine

Cont.

- There is a polymorphism of the Angiotensin Converting Enzyme gene.
- ***Warfarin susceptibility***: warfarin inhibits the vitamin K epoxide complex 1 (VKORC1)
  - Sensitivity to warfarin has been associated with the genetically determined combination of
    - Reduce metabolism of the S – warfarin by CYP2C9 polymorphic variants &
    - Reduced activity (low amounts) of VKORC1

Cont.

- There is ~40% of variability in warfarin dosing requirement
- Warfarin resistance (requirement for very high doses of warfarin) has been noted in a few people and may be related to ***variants in either CYP2C9 combined with VKORC1***.

Familial hypercholesterolemia

- It is an AD disease in which the ability to synthesize receptors for LDL is impaired.

3. Inherited disease that predispose to drug toxicity

- G6PDH
- Methaemoglobinemia
- Malignant hyperthermia
- Acute porphyrias
- Gilbert’s disease

G6PDH Deficiency

- The following drugs can produce hemolysis in G6PDH deficient patients:
  - Analgesics: aspirin
  - Antimalarials: primaquine, quinacrine, quinine
  - Antibacterials: sulphonamides, sulphones, nitrofurantoin, fluoroquinolones (ciprofloxacin)
  - Miscellaneous: quinidine, probenecid

Methaemoglobinemia

- Several xenobiotics which oxidize hemoglobin to methemoglobin including:
  - Nitrates
  - Nitrites
  - Chlorates
  - Sulphonamides
  - Sulphones
  - Nitrobenzenes
  - Nitrotoluenes
  - Anilines
  - Topical LAs

Cont.

- In certain Hb variants (HbM and HbH) the oxidized methemoglobin form is not readily converted back into reduced functional Hb
- Exposure to the above substances causes methaemoglobinemia in individuals with these Hb variants
- Similarly nitrites, chlorates, dapsone and primaquine can cause cyanosis in patients with a deficiency of **NADH methemoglobin reductase.**

Malignant hyperthermia

- Rare
- Potentially fatal complication of GA causative agent is usually an inhalational anesthetic halothane, isoflurane +/- succinylcholine
- Rx: dantrolene

Acute porphyria

- In these group of disease acute illness is precipitated by drugs because of inherited enzyme deficiencies in the pathways of heme biosynthesis.
- Most of the drugs that have been incriminated are ***enzyme inducers that raise hepatic ALA synthetase levels***.
- These drugs include: phenytoin, sulphonylureas, ethanol, griseofulvin, sulphonamides, sex hormones, methyldopa, imipramine, theophylline, rifampicin & pyrazinamide.
- Often a singe dose of one rug of this type can precipitate an acute episode. However in some patients repeated doses are necessary to provoke a reaction.

Gilbert's disease

- This is a benign chronic form of primarily unconjugated hyperbilirubinemia.
- Caused by inherited reduced activity or lack of ***hepatic conjugating enzyme uridine phosphoglucuronyl transferase (UGT1A1)***
- **Estrogens** impair bilirubin uptake & aggravate jaundice in patients with this condition, as does **protracted fasting**.
- The active metabolite of **irinotecan** is glucuronidated by UGT1A1, so irinotecan toxicity is increased in Gilbert's disease

The utility of pharmacogenetics

- Determining appropriate dosing
- Avoiding unnecessary toxic treatments
- Ensuring maximal efficacy
- Reducing ADRs
- Developing or choosing novel treatments
- Can also explain variable response to illicit drugs

Personalized medicine

- There is an emerging goal among ‘translational scientists’ to make medical practice more personalized
- Pharmacogenetics is an important step towards that goal

3. GENE BASED THERAPY
11TH/6/2019

B: DR. MUASYA

TYPED BY NAILA KAMADI

SCOPE

- Introduction
- What are genes & what can they do?
- Types of gene therapy
- Important considerations in choosing a gene delivery system
- Properties of an ideal gene transfer vector

Cont.

- Strategies for delivering genes into patients
- Types of vectors
- Clinical applications of gene therapy
- Potential complications of gene therapy
- Problems associated with gene therapy
- Controversies of gene therapy

INTRODUCTION

- Gene therapy is ***largely an experimental treatment***. It involves introducing genetic material (DNA or RNA) into a person's cells to fight disease.
- **It is not currently available outside clinical trials**.
- Delivery of naked DNA or RNA to a cell is an inefficient process & therefore most gene transfer is carried out using a vector (***carrier molecule or gene delivery vehicle***).
- These vehicles have generally been engineered from viruses by deleting some or all of the viral genome & replacing it with the therapeutic gene of interest under the control of a suitable ***promoter***.

WHAT ARE GENES & WHAT CAN THEY DO?

- Genes are the basic physical & functional unit of heredity.
- They are carried on ***chromosomes***.
- They are specific sequences of bases that encode instructions on how to make proteins.
- It is the proteins that perform most life function & even make up majority of cellular structures.

TYPES OF GENE THERAPY

Gene therapy can target:

- ***Somatic/ Body cells***: recipient genome is changed but the change is not passed to the next generation.
- ***Germ cells (egg & sperms); Germline***: newly introduced gene is passed on to offspring.

IMPORTANT CONSIDERATIONS IN CHOOSING A GENE DELIVERY SYSTEM

- ***Capacity***: how much DNA it can carry.
- ***Transfection efficiency***: ability to enter & become utilized by cells
- ***Lifetime of transfected material***: determined by the lifetime of the targeted cells e.g. skin epithelial cells shed off every 2 – 3 weeks; hence it is difficult for gene therapy delivered to them to be to be permanent
- ***Safety***: esp. in the case of viral delivery systems

PROPERTIES OF AN IDEAL GENE TRANSFER VECTOR

- ***Safe***
- ***Highly efficient***: should insert the therapeutic gene into a high proportion of target cells
- ***Selective***: it should lead to expression of the therapeutic protein in the target cells but not to the expression of viral proteins
- ***Persistent expression***: provided that the cell into which it is inserted is itself long lived the vector should ideally cause persistent expression and this avoids the need for repeated treatment
  - This consideration can be a problem in some tissues with cells that continuously turn over s.a. GIT, airway & skin epithelium

MAIN STRATEGIES FOR DELIVERING GENES INTO PATIENTS

- There are 2 main strategies for delivering genes into patients:

I. In vivo strategy

II. Ex vivo strategy

I. In vivo strategy

- The vector containing the therapeutic gene is injected into the patient either:
  - IV: some form of organ or tissue targeting is required e.g. radio – labelled iodine targeting the thyroid gland.
  - Directly into the target tissue e.g. malignant tumor, retina.

Steps in in vivo gene therapy

- The DNA (Gene) is prepared either with viral or non – viral production.
  - In viral production, the DNA is encapsulated in an adeno – associated virus (for instance).
- Direct administration into patient follows.
- Protein is expressed that affects the patient's phenotype.

II. Ex vivo strategy

- Here, the patient's cells (e.g. stem cells from bone marrow or myoblasts from a biopsy of striated muscles) are removed & treated with the vector in the lab.
- The genetically altered cells are then injected back into the patient.

The Ex vivo technique

- Remove cells from patient.
- In lab, alter virus so it does not reproduce.
- Insert therapeutic gene into virus.
- Mix altered virus with cells from patient to allow genetic alteration of patient's cells.
- Inject altered patient's cells back into the patient.
- Desired protein or hormone is expressed.

TYPES OF VECTORS:

Viral

- Integrating
- Non – integrating

Non – viral

- Liposomes
- Microspheres
- Plasmid DNA

I. Viral Vectors

- Many gene delivering strategies aim to capitalize on:
  1. Capacity of viruses to alter the transcriptional machinery of the cells they invade.
  2. The ability of viruses (in some cases) to fuse with the host genome
- NB: Many of these viruses are pathogenic therefore they are usually modified & made ***replication – defective*** to avoid toxicity.

Specific viral vectors:
DNA or RNA genome derived

RNA viral vectors

- Retroviruses
- Lentiviruses
- Human foamy virus
- Alpha viruses

DNA viral vectors

- Adenovirus
- Adeno – associated virus (AAV)
- Herpes simplex virus
- Poxvirus (vaccine virus)

Specific viral vectors fall into one of 2 main categories

a. ***Integrating vectors***: insert themselves into the recipient's genome; Therefore the therapeutic gene is passed down to each daughter cell during division.

b. ***Non – integrating vectors***: often (although not always) form an extrachromosomal genetic element.

a. Integrating vectors

- Such as ***γ – retroviral vectors & lentiviral vectors*** are generally used to transfect actively dividing cells because they are stably inherited.
- However they may carry the risk for ***insertional mutagenesis*** (with clinical oncogenic transformations, i.e., ***secondary malignancies*** reported with the use of retroviruses).
  - Types of retroviruses include: Lentivirus, HIV, Simian Immunosuppressive virus (SIV)
  - It is possible to use a disabled version of HIV which, unlike other retro viruses, can infect non – dividing cells such as adult neurons.

b. Non – integrating vectors

- Such as ***Adenovirus, Adenovirus Associated Virus (AAV)***.
- These can be used to transfect non – dividing cells such as adult neurons or slowly dividing cells.
- However they are quickly lost from cells that divide rapidly e.g. in the case of adenoviral vectors.

TABLE 91e-1 CHARACTERISTICS OF GENE DELIVERY VEHICLES

	Viral Vectors						
Features	**Retroviral**	**Lentiviral**	**Adenoviral**	**AAV**	**Human Foamy Virus**	**HSV-1**	**Alpha Viruses**
Viral genome	RNA	RNA	DNA	DNA	RNA	DNA	RNA
Cell division requirement	Yes	G_1 phase	No	No	No	No	No
Packaging limitation	8 kb	8 kb	8–30 kb	5 kb	8.5 kb	40–150 kb	5 kb
Immune responses to vector	Few	Few	Extensive	Few	Few	Few in recombinant virus	Few
Genome integration	Yes	Yes	Poor	Poor	Yes	No	No
Long-term expression	Yes	Yes	No	Yes	Yes	No	No
Main advantages	Persistent gene transfer in dividing cells	Persistent gene transfer in transduced tissues	Highly effective in transducing various tissues	Elicits few inflammatory responses, nonpathogenic	Persistent gene expression in both dividing and nondividing cells	Large packaging capacity with persistent gene transfer	Limited immune responses against the vector
Main disadvantages	Theoretical risk of insertional mutagenesis (occurred in multiple cases)	Might induce oncogenesis in some cases (not yet observed)	Viral capsid elicits strong immune responses	Limited packaging capacity	In need of a stable packaging system	Residual cytotoxicity with neuron specificity	Transduced gene expression is transient

Abbreviations: AAV, adeno-associated virus; HSV, herpes simplex virus; SV, sarcoma virus.

II. Non – viral vectors

- Include:
  a. Liposomes
  b. Microspheres
  c. Plasmid DNA

a. Liposomes

- Involve creation of an ***artificial lipid sphere with an aqueous core***.
- Liposomes carry the therapeutic DNA and are capable of passing it through the target cell's membrane.

Advantages & disadvantages of liposomes

Advantages

- DNA/ lipid complexes are easy to prepare
- There is no limit to the size of genes that can be delivered
- Carrier systems lack protein therefore they may evoke much less immunogenic response

Disadvantages

- Much less efficient than viruses

Clinical use of liposomes

- Have been used to deliver the genes for ***HLA – B7, IL – 2 & CFTR (cystic fibrosis transporter regulator)***.
- Their direct injection into solid tumors (e.g. melanoma, breast, kidney & colon cancers) can achieve high local concentrations within the tumor.

b. Microspheres

- Biodegradable microspheres made from ***polyanhydride copolymers of fumaric or sebasic acids*** can be loaded with plasmid DNA.
- A plasmid with bacterial **β galactosidase** activity formulated in this way can be given by mouth resulting in systemic absorption & expression of bacterial enzyme in the rat liver.
- This is raising the possibility of ***oral gene therapy***.

b. Plasmid DNA

- Basically naked DNA.
- It enters the nucleus of some cells & is ***expressed even though much less efficiently than when it is packaged in a vector***.
- Such DNA carries no risk of viral replication & is not usually immunogenic (***although autoantibodies to DNA may occur in conditions like SLE***)
- However it cannot be targeted to a cell of interest.

Cont.

- There is a great interest in the possibility of using naked DNA for vaccines as a small amount of foreign protein can stimulate an immune response, i.e.:
  - 2 DNA recombinant Hepatitis B vaccines are in clinical use
    - Both are highly immunogenic in children & adults (but most vaccines are given in children)
  - A vaccine for influenza
  - Long term targets that are under investigation: malaria, TB, chlamydia, *Helicobacter pylori*

CLINICAL APPLICATIONS OF GENE THERAPY

I. Genetic diseases: Inherited immunodeficiency disorders among others.
II. Cancer
III. Vascular disease
IV. Infectious diseases
V. Other diseases.

Rang & dale 8ED fig 59 – 4 for genes delivered, vectors & techniques used for different disease

I. Genetic diseases: Inherited immunodeficiency disorders

- Include:
  a. X – linked Severe Combined Immunodeficiency (SCID)
  b. Adenosine Deaminase Deficiency SCID
  c. X – linked chronic granulomatous disease

a. X – linked Severe Combined Immunodeficiency (SCID)

- Results from mutations in the ***gene IL – 2RG*** encoding the common γ chain subunit (CD132) of a cytokine receptor required for normal development of T & NK cells.
- Characterized by dysregulation of T & NK cell development.
- Affected infants present in the 1st few months of life with overwhelming infections &/or FTT.

Trials

- Out of 20 infants treated in these trials, 18 achieved correction of the immunodeficiency disorders, with complete reconstitution of the immune system.
- Unfortunately 5 later developed a leukemia like disorder and one died.
- These studies have therefore, demonstrated that insertional mutagenesis leading to cancer could occur.
- These were the first gene therapy trials.

Cont.

- Adenosine Deaminase Deficiency SCID: Success has also been achieved in gene therapy trials.
- X – linked chronic granulomatous disease: Has been successfully treated using a ***retroviral technique*** to deliver a functional version of the mutated NADPH oxidase protein.

Other Genetic Diseases

- Leber’s congenital amaurosis
- Lipoprotein lipase deficiency
- Thalassemia

Leber’s congenital amaurosis

- Form of inherited blindness.
- Associated with a mutation in a gene that produces retinal pigment.
- It has been cured using ***an AAV vector bearing a clonal DNA encoding the intact gene***.

Lipoprotein lipase deficiency

- ***Glybera*** is an AAV construct that delivers a correct copy of lipoprotein lipase to patients lacking this enzyme.
- A very rare disorder manifesting with:
  - Recurrent abdominal pain
  - Acute pancreatitis
  - Eruptive xanthomas (in about 50% of patients)
  - Lipemia retinalis
  - Hepatosplenomegaly

Cont.

Thalassemia:

- Success in patients with thalassemia has been observed using the **β globulin gene**.

Clinical trial using recombinant AAV vectors are ongoing for the following conditions:

- Muscular dystrophy
- α – 1 antitrypsin deficiency (A1AD)
- Hemophilia B

Cont.

Other inherited diseases amenable to gene therapy via hematopoietic stem cells are:

- Wiskott – Aldrich Syndrome (WAS)
- Sickle Cell Disease

ii. Gene therapy for cancer & related disease

- Comprise 70% of all trials.
- As a general rule they are less toxic when compared with conventional cancer chemotherapeutic therapy.

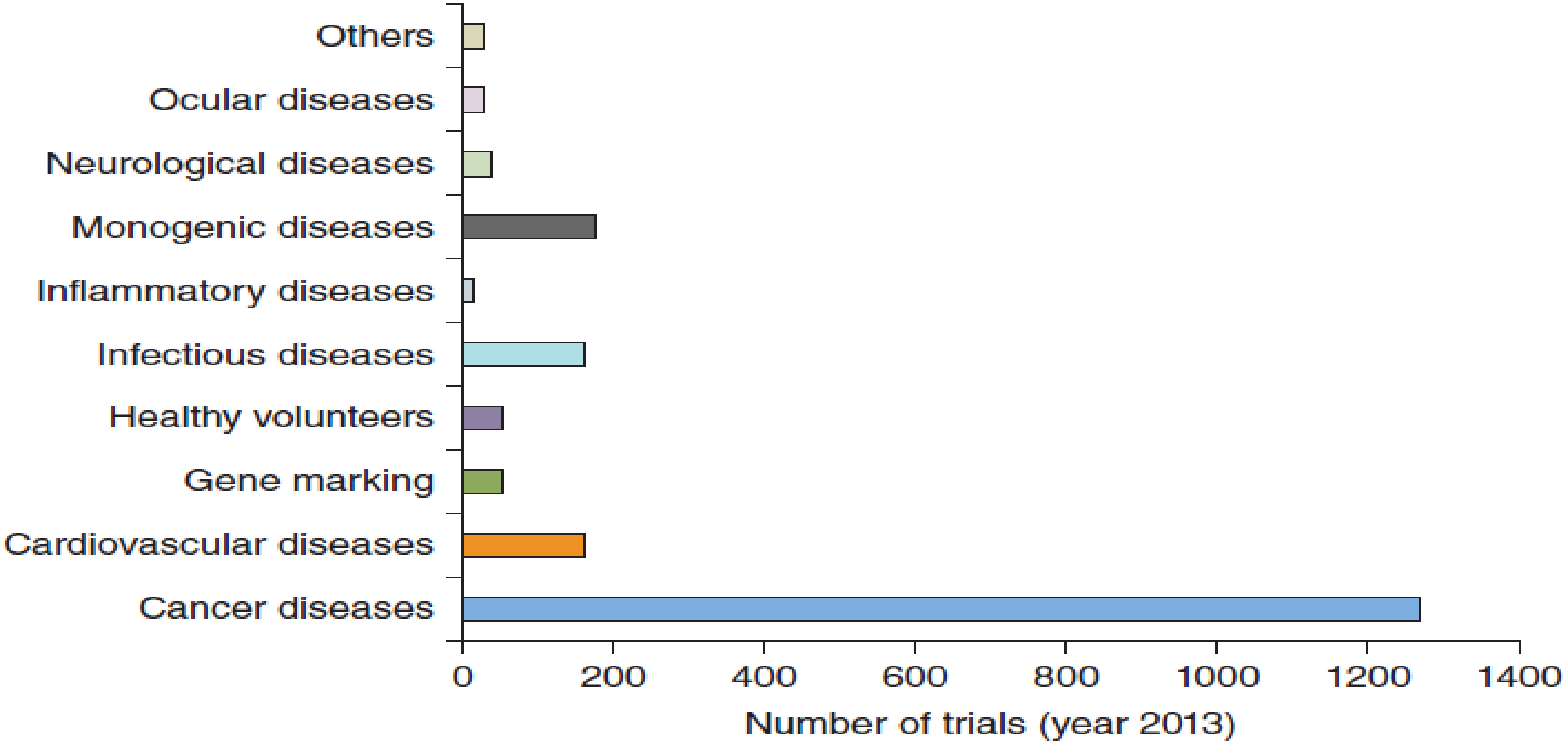


FIGURE 91e-1 Indications in gene therapy clinical trials. The bar graph classifies clinical gene transfer studies by disease. A majority of trials have addressed cancer, with monogenic disorders, infectious diseases, and cardiovascular diseases the next largest categories. *(Adapted from SL Ginn et al: J Gene Med 15:65-77, 2013. Published*

Classification of cancer gene therapies

a. Local approaches

- Suicide gene/ prodrug
- Suppressor oncogene
- Oncolytic virus

b. Systemic approaches

- Chemo protection
- Immunomodulation
- Anti – angiogenesis

a. Local approaches

Local delivery of a prodrug or suicide gene that increases sensitivity of tumor cells to cytotoxic drugs

- A frequently used strategy is intra – tumoral injection of an adenoviral vector expressing the ***thymidine kinase gene***.
- Cells that take up & express the thymidine kinase gene can be killed after the administration of ganciclovir that is phosphorylated to a toxic nucleoside by tyrosine kinase.
- This strategy was initially used for Rx of aggressive brain tumors (e.g. glioblastoma Multiforme, GBM) where the cycling tumor cells were affected & the non – dividing normal neurons were not.
- It is being explored for ***locally recurrent prostate cancer, breast & colon cancer***.

Cont.

Use of adenoviral mediated expression of the tumor suppressor p53 mutated in a wide variety of caners

- This strategy has shown complete & partial response in the following after direct intra tumoral injection of vector:
  - Squamous cell carcinoma of the head & neck region.
  - Esophageal cancer
  - Non – small cell lung cancer (NSCLC)

Oncolytic viruses

- These selectively replicate in tumor but not in normal cells.

b. Systemic approaches

- Metastatic disease is the source of mortality in most cancers.
- There has been considerable interest in developing systemic gene therapy approaches.
- They include:
  - Chemo protection
  - Immunomodulation
  - Anti angiogenesis

Cont.

Chemoprotection

- Involves the use of gene transfer to protect normal cells from toxicities of chemotherapy.
- An example is the transduction of hematopoietic stem cells with genes encoding resistance to chemotherapeutic agents, including multidrug resistant gene (MDRI) or gene encoding ***O^6 – Methyl guanine DNA Methyltransferase (MGMT)***

Cont.

Immunomodulation

- Promotes more efficient recognition of tumor cells by the immune system.
- Approaches:
  - Transduction of tumor cells with immune enhancing genes encoding cytokines, chemokines or costimulatory molecules
  - Ex vivo manipulation of dendritic cells to enhance the expression of tumor antigens.
- Success has been seen with lentiviral transduction of autologous lymphocytes in treatment of :
  - Refractory leukemia
  - CD 19 expressing B cell malignancies

Anti – angiogenesis

- Gene transfer strategies that mediate inhibition of angiogenesis.

iii. Gene therapy for vascular disease

- Strategies were put in place to increase blood flow to skeletal & cardiac muscle but the results were not good.
- The following were used:
  - VEGF
  - FGF
  - Hypoxia inducible factor
- There was no change in amputation frequency (in Peripheral Arterial Disease) or cardiovascular mortality (in ischemic heart disease) observed.

Cont.

- Recent studies have used AAV vectors to develop a therapeutic approach for individuals with CCF:
- Preclinical studies: vectors encoding sarcoplasmic reticulum ATPases demonstrated improvement in a swine model of chronic Left Ventricular Heart Failure.
- Larger studies are ongoing.

iii. Gene therapy for infectious disease

- DNA vaccines are used.
- There is a potential for therapy for HIV by rendering stem cells that differentiate to immune cells resistant to HIV before they mature.

Other diseases

- Gene therapies are being explored for ***neurodegenerative diseases*** such as ***Parkinson's disease, Alzheimer's disease.***

TABLE 91e-2 POTENTIAL COMPLICATIONS OF GENE THERAPY

Gene silencing – repression of promoter
Genotoxicity – complications arising from insertional mutagenesis
Phenotoxicity – complications arising from overexpression or ectopic expression of the transgene
Immunotoxicity – harmful immune response to either the vector or transgene
Risks of horizontal transmission – shedding of infectious vector into environment
Risks of vertical transmission – germline transmission of donated DNA

PROBLEMS ASSOCIATED WITH GENE THERAPY

- ***Short lived***
  - Hard to rapidly integrate therapeutic DNA into genome
  - Rapidly dividing nature of cells prevent long term gene therapy effects; multiple cycles of therapy may be required.
- ***Immune response***
  - New things introduced into the body elicit an immune response.
  - The response is more pronounced when a repeat offender is introduced.

Cont.

- ***Problems associated with viral vectors***
  - Toxic immune or inflammatory response to vector.
  - May cause disease once inside body
- ***Multigene disorders***
  - Heart disease, HTN, Alzheimer's disease, arthritis, DM
  - Hard to treat because >1 gene needs to be introduced
- ***Malignancy***
  - May induce a tumor if integrated in a TSG because of insertional mutagenesis.

CONTROVERSIES

- Most powerful: ***human germline gene therapy***
- Somatic gene therapy targets human body cells (BM or blood cells). Germline therapy alters genetic material in sperms & eggs.
- Hence any change made by the germline gene therapy will be passed on to the next generation.

Cont.

- ***Germline*** of a mature or developing individual is the line (sequence) of germ cells that have genetic material that may be passed to a child.
- Germ line cells are immortal, in the sense that they can reproduce indefinitely.
- As a rule, therefore, ***germline gene therapy is not advocated for in most parts of the world***.

DRUG INTERACTIONS
21/6/2019

BY: DR. INDALO

DRUG INTERACTIONS

- May occur when 2 or more drugs are given at the same time.
- Effects of one drug may be altered by the administration of another drug, herbal medicine, food, drink or environmental chemical agents.

DI - RESULT

- Greater than (potentiation, synergism, supra-additive), the same as (addition, summation) or smaller than (antagonisn, infra-additive) the sum of effects of individual drugs.

DI

- **CONSEQUENCE → Beneficial or adverse.**
- **SITE → External or internal**

DIs

- **May be employed:**
  - **to improve therapeutic effect e.g. probenecid and penicillin; codeine and paracetamol; ampicillin and salbactam; Losartan and HCT; etc**
  - **in management of poisoning e.g. activated charcoal to reduce further absorption of drugs; urine alkalization/acidification in acidic & basic drug poisoning respectively; naloxone in opioid poisoning; flumezanil in benzodiazepine poisoning; etc**
- **Some DIs are not desirable**

DI - CAUSES

- Very ill patients who get more than one drug.
- Elderly - usually have more than one pathology.
- One patient seeing more than one doctor for the same health problem.
- Many patients take OTC (non prescription) drugs e.g. St.John's Wort (natural remedy for depression) interacts with warfarin, digoxin ~ induces some isoforms of Cyt P450 enzymes. Ask patient which other drugs (prescription or not) they are taking
- Consumption of other peoples prescribed drugs.
- Personal factors i.e. smoking, drinking can affect p'dynamic and p'kinetic properties of drugs.

DI - INCIDENCE

7 – 20% DI are adverse → about 2% admissions due to adverse DI.

Incidence higher in selected gp of patients:-

(i) Anticoagulant therapy – 10% may experience noticeable interaction

(ii) Patients on drugs with low T.I i.e. where plasma drug level monitoring is required.

[Death can occur as a result of DI]

DI - INCIDENCE

(iii) Related to number of drugs administered:-

No of dugs interactions	% of P with
5	4.2
6-10	7.4
11-15	24
16-20	40
21 or more	45

DI

- **Knowledge of drug interactions enables the physician to minimize or prevent drug toxicity by adjustment of the dosage or schedule of drug administration or by choice of an alternative drug.**

(DI) MECHANISMS - P'DYNAMIC

- Occur when drugs have similar or antagonistic pharmacological effects or side effects on a physiological system.
- May be due to competition at receptor sites or occur between drugs acting on the same physiological system
- Usually predictable from knowledge of the p'cology of interacting drugs
- Interactions demonstrated with one drug are likely to occur with related drugs.
- Occur to a greater extent in most patients who receive the interacting drugs

PHARMACOKINETIC DIs

- One drug affects effect of the other by altering its ADME thus increasing or reducing the amount of drug available to produce its pharmacological effects.
- Not usually predictable
- Many of them affect small proportion of patients taking the combination of drugs.
- Interactions occurring with one drug cannot be assumed to occur with related drugs unless their p'kinetic props are known to be similar.

DI - P'DYNAMIC

- **Warfarin (coumarin anticoagulant)/Vitamin K → antagonism**
- **Warfarin/ASA → synergism**
- **Tricyclic antidepressants/benzhexol → increased intensity of SE (anticholinergic)**
- **Amphetamine like drugs (anorectics)/MAOIs (antidepressants) → enhanced NA response**

DI – P’dynamic

- Tricyclic antidepressants/guanethidine →antagonism
- Aminoglycosides/penicillins
- Cyclosporin/aminoglycoside
- Trimethoprim/sulphamethoxazole

DI – P'KINETIC (ABSORPTION)

- Rate and/or extent may be affected. Important when both affected
- Rate important when rapid rate of action required e.g analgesics, anti-asthmatics single doses.
- Extent → decrease in fraction absorbed is equivalent to reduced dose.

DI (GIT)PHYSICOCHEMICAL INTERACTIONS

- Changes in GIT pH → antacids/basic drugs
- Chelation → tetracycline/iron, calcium, magnesium, aluminium etc, ergotamine/caffeine
- Ion exchange resin binding → cholestryramine/ASA, warfarin etc
- Adsorption → kaopectate/lincomycin
- Adsorption → activated charcoal/sulfonamides
- Dissolution in non-absorbable material

DI - GIT

- Gastric motility → Anticholinergics and ganglion blockers reduce absn of many drugs due to lower efficiency of mixing, delay in stomach emptying and increased decomposition e.g penicillin, erythromycin, BDZ etc.
- Changes in bacterial flora → tetracycline/warfarin
- Drug induced mucosal changes caused by colchicine

DI - DISTRIBUTION

- **Blood flow e.g propranolol decreases CO → decreased BF.**
- **Active transport to site of action e.g TCA and guanethidine**
- **Tissue uptake or binding**
- **Serum protein binding → phenylbutazone/warfarin, sulfaphenazole/tolbutamide.**

POINTS – DI DISTRIBUTION

- Binding is reversible depending on nature of the drug, [D] in plasma, and [P]
- Displacement occurs if same sites involved
- Greatest problem with drugs which are highly bound
- Acidic drugs are generally strongly bound to plasma protein (particularly albumin) and displace others

DI – BIOTRANSFORMATION (INHIBITION)

- Allopurinol/azathioprine,6-mecaptopurine
- MAOI/tyramine
- Cimetidine/benzodiazepines
- Chloramphenical/phenytoin
- Dicoumarol/phenytoin, tolbutamide, chlorpropamide
- Ketoconazole/cyclosporine
- Itraconazole/pimozide
- L-dopa/carbidopa
- Simvastatin/erythromycin, diltiazem, verapamil, amiodarone, grapefruit juice ~ increase simvastatin plasma levels

DI – BIOTRANSFORMATION (INDUCTION)

Many drugs induce size and enzyme content in endoplasmic reticulum.

- **Takes 1-2 weeks to develop and 3-4 weeks to go back to normal after ceasation.**
- **Phenobarbitone/warfarin**
- **Aminoglutethimide/warfarin**
- **Rifampin/warfarin**
- **Carbamazepine/theophylline**

DI - EXCRETION

- GF – increased by displacement from albumin
- Tubular secretion – indomethacin/probenecid, penicillin/probenecid
- Tubular reabsorption decreased by diuretics; alkalinizers for acidic drugs; acidifiers for weak bases.

DI – DRUGS/CONTENTS OF FOOD

- MAOIs/Tyramine (cheese, tomato, yogurt, pears, wines, beer, avacado etc)
- Alcohol/barbiturates, antihistamines, benzodiazepines, metronidazole etc
- Tetracycline/milk (dairy products)

HOW TO DEAL WITH DI

- Drugs exert a similar effect → possible toxicity. If one or both have narrow TI dose may need to be reduced.
- Drugs exert opposite effect → possible decrease in effect. Avoid if possible.
- Drugs may interact at receptor → increase or decrease dose of another
- One drug may suggest a disease which may affect handling of the other → adjust dosage

DEALING WITH DI cont..

- Drugs have similar side effects → decrease dose or change therapy.
- Effect on absorption of the other → separate administration interval.
- Displacement from plasma protein binding sites → important when the drugs in question have narrow TI or small Vd
- Inhibit or enhance met of the other → important when drugs have narrow TI; prodrugs.
- Effect on excretion of the other → extend dose interval.
- Monitor patients intensively to see what is going on.

Computer programmes which when you prescribe drugs warns you of side effects or interactions

ADVERSE DRUG REACTIONS

BY: DR. INDALO

- **Drug typically produces numerous effects, but usually only one is sought as the primary goal of Tx. The other effects are referred to as undesirable for that therapeutic indication**
- **DEF: Any noxious, unintended & undesired effect of a drug which is observed at doses usually administered in man**
- **The def. excludes cases of overdose, drug abuse or therapeutic errors**

- **DEF: Side effect is an action other than the intended therapeutic effect of a drug. May be neutral, beneficial or harmful**
- **A harmful side effect is an adverse drug reaction**

INCIDENCE OF ADRs

- Hospital patients 10-20%
- Deaths in hospital in-patients 0.24-2.9% due to ADRs
- Hospital admissions 0.3-5.0% are due to ADRs

ADRs

- Result of an interaction between the characteristics of the drug administered & some inherent or acquired characteristics of the patient which determine his pattern of response to drugs
- Some are determined by the physicochemical or P'kinetic characteristics of the drug, formulation, dose, rate and route of admn
- Others are determined chiefly by the patients characteristics such as genetic, physiological or pathological
- For some both drug & patient variable are important

Adverse drug reactions can be dose-related, not dose-related or idiosyncratic

NB: IDENTIFICATION OF THE TYPE OF ADR ~ DOSE OR NOT DOSE-RELATED IS IMPORTANT BECAUSE IT ALLOWS PRACTICAL DECISIONS CONCERNING Tx OF AN INDIVIDUAL PATIENT &/OR PREVENTION OF ADRs

Severity of ADRs is classified as:

- **Mild**
- **Moderate**
- **Severe**
- **Lethal**

CLASSIFICATION OF ADVERSE DRUG REACTIONS

Type of reaction	Mnemonic	Features	Examples	Mx	
Dose related	**Augmented**	**Common; related to p'ological action of drug; predictable; low mortality**	**Toxic effect e.g. of digitoxin; serotonin syndrome with SSRIs. SEs e.g. antichlinergic effects of TCAs**	**Reduce dose or withhold. Consider effect of concomitant therapy**	
Non-dose related	**Bizzare**	**Uncommon; not related to pharm effect; unpredictable; high mortality**	**Immunological reactions e.g pen hypersensitivity; idiosyncratic rns e.g. acute porphyria, malignant hyperthermia, pseudoallergy e.g. ampicillin rash**	**Withhold and avoid in future**	

Type of reaction	Mnemonic	Features	Examples	Management
Dose related and time related	Chronic	Uncommon; related to cummulative dose	Hypothalamic-pituitary-adrenal axis suppression by corticosteroids	Reduce dose or withhold; withdrawal may have to be prolonged
Time related	Delayed	Uncommon; usually dose-related; occurs or becomes apparent sometime after the use of the drug	Terratogenesis, (e.g vaginal adenocarcinoma with diethylstilbestrol) ; carcinogenesis; tardive dyskinesia	Often intractable

Type of reaction	Mnemonic	Features	Examples	Management
Withdrawal	End of use	Uncommon; occurs soon after withdrawal of the drug	Opiate withdrawal syndrome; myocardial ischaemia (beta blocker withdrawal)	Reintroduce and withdraw slowly
Unexpected failure of therapy	Failure	Common; dose-related; often caused by drug interactions	Inadequate dosage of an oral contraceptive particularly when used with specific enzyme inducers	Increase dosage; consider effect of concomittant therapy

ALLERGIC OR HYPERSENSITIVITY REACTIONS

4 main clinical types:

- **Type 1 (anaphylactic)**
- **Type 2 (cytotoxic)**
- **Type 3 (immune-complex mediated)**
- **Type4 (cell-mediated)**

Hepatotoxicity

- Liver is the major site of drug biotransformation → hepatocytes are exposed to reactive metabolites formed by cytP450 enzyme activity e.g. the reactive metabolite of paracetamol

Nephrotoxicity

- Kidney exposed to high concentrations of drugs/metabolites as the urine is concentrated
- Can be produced by general mechanisms of cell injury, which can cause papillary &/or tubular necrosis

Adverse effects associated with reproduction

- Impairment of spermatozoal production or function e.g. MAOIs, cytotoxic drugs etc
- Teratogenesis → see dugs to avoid in pregnancy
- Adverse reactions to drugs in breast milk

Teratogenesis & drug-induced fetal damage

- Less than 1% of congenital defects attributable to drugs given to the mother.
- Gross malformations produced only if teratogens act during organogenesis
- MA of teratogens may be due to DNA damage
- New drugs usually tested in pregnant female lab animals before clinical studies

Thalidomide teratogenesis

Day of gestation	Type of deformity
21-22	Malformation of ears Cranial nerve defects
24-27	Phocomelia of arms
28-29	Phocomelia of arms and legs
30-36	Malformation of hands Anorectal stenosis

The thalidomide story

- 1961 – William McBride, an obstetrician reported ↑ed number of congenital malformations associated with use of thalidomide
- Marketed in Europe as a hypnotic ‘safe’ in pregnancy!
- Fewer thalidomaide induced phocomelia in USA than in Europe ~ FDA delayed marketing approval because of concerns about toxicity in acute animal studies
- OTC in West Germany (most affected)

EPIDEMIOLOGY OF ADRs

Drug monitoring methods – information on ADRs collected using such methods as:-

- **Spontaneous communication to National Drug Monitoring Centers**
- **Cohort studies**
- **Case control studies**

FACTORS ASSOCIATED WITH ADRs

AGE:

Older people more susceptible

- **Usually have multiple pathology ~ many drugs → DIs etc**
- **Have impaired drug elimination &/or increased receptor sensitivity to drugs**
- **More sensitive to powerful analgesics; higher risk of developing toxicity with many drugs e.g. digitalis, diuretics etc**
- **The Newborn, particularly the premature is more sensitive to some ADRs ~ incomplete development of drug metabolizing enzymes**

Ways to minimize adverse SEs

- Extend pre-marketing human studies.
- Phase the marketing of new drugs, with appropriate monitoring of safety and efficacy
- Prescribe drugs for a finite period; review a patient's drug prescriptions periodically.
- Individualise dosage, especially for elderly patients
- Review the patient's nutrition, in the light of drugs prescribed

SAFETY EFFICACY OF MEDICINES

- Most drugs are selectively-toxic chemicals
- Few drugs exhibit a single pharmacological/physiological effect
- Adverse side effects are properties of drug-patient-environment interactions
- No drug can be absolutely safe for all patients
- Drugs confer benefit. The benefit/risk ratio should be acceptable to the individual patient

IMMUNOPHARMACOLOGY

BY: DR. OMONGE

PRINCIPLES OF PRESCRIPTION WRITING

BY: DR. INDALO

TYPED BY NAILA KAMADI

The trouble is, you always think you have time until it is gone.

It is oft while facing walls of water, that your mortality strikes you to the bone.

Then as you are swept away, you realize it is not you on the throne.

#Every_Knee_Shall_Bow

#Jesus_Is_King

2. CARDIOVASCULAR THERAPEUTICS LEVEL VI MBCHB 2019

COMPILED BY NAILA KAMADI

OUTLINE

- Rational use of antihypertensives
- Management of cardiac emergencies
- Drugs for IHD & hyperlipidemia
- Management of CCF
- Actions and uses of thrombolytic agents
- Treatment of VTE
- Procoagulants & management of bleeding
- IV Fluids

1. RATIONAL USE OF ANTIHYPERTENSIVES 25/1/2019

BY: DR. E. OMONGE

DIAGNOSIS

- Usually asymptomatic
- Diagnosis is made after recording repeated elevated BP > $\frac{140}{90}$ mmHg
- Optimum control: $\frac{130}{80}$ mmHg
- The risk of adverse cardiovascular events increases with BP

RISK OF HTN DEPENDS ON

- Race
- Gender
- Age
- Smoking
- Alcohol consumption
- DM
- Hyperlipidemia
- Familial history

CONVENTIONAL DEFINITIONS

- The risk of end organ damage is reduced at BP < 120/80 mmHg but it increases with progressive rise in BP.
- Severe HTN > 210/120 (malignant HTN) is essentially an **arteriolopathy** that manifests with rapid target organ damage:
  - Hypertensive nephropathy → renal failure
  - Hypertensive encephalopathy → CVA
  - Hypertensive retinopathy → retinal changes (***a funduscopy is diagnostic for malignant HTN with target organ damage***)
  - MAHA

REVIEW THE RAAS

- Actions of angiotensin
  - Potent vasoconstrictor
  - Increases production of aldosterone → Salt and water retention
  - Dipsogenic
  - Mitogenic → hyperplasia & hypertrophy of vascular smooth muscle

RATIONALE

- In a hypertensive that is ≥ 55 y/o or in a black patient of any age:
  - Monotherapy: thiazide (HCTZ, chlorothalidone) or thiazide – like diuretic (indapamide)
  - Combination therapy: dihydropyridine CCB (Nifedipine) for vasodilatation

CONT.

- In a hypertensive that is < 55 y/o or in a white patient of any age:
  - Beta blocker to inhibit renin production OR
  - ACE –I (or ARB if ACE – I intolerant e.g. dry cough)

NB

- Never give a loop diuretic e.g. frusemide to an antihypertensive unless they are in HF.
- This is because it causes brisk diuresis that results in hypovolemia.
- Hypovolemia stimulates the production of renin & activation of angiotensin due to a reduction in CO.
- This results in a worsening of the HTN.

CONSIDERATIONS IN THE PRESENCE OF TARGET ORGAN INVOLVEMENT

- Hypertensive nephropathy: ACE –I are preferred since they are renoprotective.
- Ischemic Heart Disease: Avoid vasodilators since they produce a reflex tachycardia that overworks the ischemic myocardium while reducing the diastolic myocardial perfusion. This may result in an acute myocardial infarction (AMI)

COMPLICATIONS OF UNTREATED HTN (BP > 140/90)

- Vascular pathology: LVH, coronary thrombosis, AMI, cerebrovascular events (stroke)
- Renal insufficiency
- Dissecting abdominal aortic aneurysm (AAA)
- CCF
- Sudden cardiac death (SCD)

AETIOLOGY OF HTN

- 90% of cases are idiopathic i.e. essential/ primary HTN & they warrant long – term treatment.
- Secondary HTN:
  - Renal artery stenosis: auscultate the costovertebral angle for bruits.
  - Coarctation of the aorta: radio –femoral delay in pulses
  - Phaechromocytoma: rapidly undulating elevated BP
  - Cushing's syndrome
  - Primary aldosteronism
  - Kidney disease → PCKD

APPROACH TO CARE

- Diastolic 85 –94 mmHg: non – drug methods
- Reduction to < 85mmHg confers more protection than 90mmHg
- Lower levels of BP are desired in diabetics.
- Drugs may either be used singly or in combination.

CONT.

- Exclude secondary causes
- Assess the severity
- Consider A/Es of drugs used
- Cost
- Convenience: e.g. captopril TDS vs. enalapril OD
- Complications
- Comorbidity: if diabetic give ACEI which is renoprotective

DIURETICS

- Deplete Na^+ & volume
- Ensure you restrict salt
- Reduction of Na^+ coupled with eventual reduction of PVR
- **Indapamide** is a non – thiazide sulfonamide diuretic with a VD effect on arterial circulation (act on Ca^{2+} channels on vessel walls)
- HTN + HF: use loop diuretic like **frusemide** which in addition to reducing TBV also venodilates.
- **Amiloride** inhibits SMC contraction in response to stimuli

CONT.

- Adequate for mild –moderate HTN & lowers BP by 10 –15 mmHg
- Used in combination
- Uses:
  - HTN → thiazides
  - CHF → loop diuretics
  - If in renal failure add K^+ sparing diuretic e.g. spironolactone

A/E

- Hypokalemia
- Hypomagnesemia
- Hyperglycemia
- Hyperuricemia
- Hyperlipidemia
- RCC

CENTRALLY ACTING SYMPATHOPLEGICS

- Reduce sympathetic outflow
- Only used in hypertensive urgency
- A/E of methyldopa: ED, depression, xerostomia

ADRENOCEPTOR ANTAGONISTS

- Propranolol: HTN, IHD
- Used for mild to moderate HTN
- Prevent reflex tachycardia, reduce mortality in CCF
- Act by beta blockade, inhibit renin production
- Toxicity: bradycardia, bronchoasthma, DM, peripheral vascular insufficiency
- For HTN emergencies: labetalol

VASODILATORS

- Hydralazine, minoxidil, nitroprusside
- Best used as combination
- Hydralazine: dilates arterioles and veins useful in severe HT
- Diazoxide: HTN emergencies (aim is to bring BP down to a DBP of about 110 mmHg over 4h; bringing the BP too low too rapidly esp. in the setting of a stroke may be fatal)

CCBS

- Inhibit Ca^{2+} influx in smooth muscle cell
  - Dihydropyridine vs. non – dihydropyridines
  - Dihydropyridine: cause reflex tachycardia (used for HTN but be careful if patient has IHD)
- Non –dihydropyridine (verapamil, Diltiazem): cause bradycardia (used for anti –arrhythmic effect)
- Act on ion channels (largely on the L –type channel); influx of ions results in muscle contraction and neurohormonal activation

ACEI/ARBS

- Consider in:
  - Renal failure
  - Heart failure (MUST)

KNOW

- Common anti –hypertensive drugs and their adverse effects
  - Thiazides: urinary frequency, gout, glucose intolerance, hypokalemia, hyponatremia
  - ACEI: dry cough, 1st dose hypotension, teratogenicity, reversible renal dysfunction (in presence of renal artery stenosis)
  - ARBs: teratogenicity, reversible renal dysfunction (in presence of renal dysfunction)

CONT.

- CCBs: ankle edema
- Beta blockers: bronchospasm, fatigue, cold hands and feet, bradycardia
- Alpha adrenoceptor antagonists: first dose hypotension (start with captopril and see if the pressure drops drastically; captopril has a short half life; once you have established no hypotension, choose a longer half life one)

2. MANAGEMENT OF CARDIAC EMERGENCIES

22/1/2019

BY: DR. OCHANDA

Cardiac emergencies include

- Cardiogenic shock
- CCF
- Pulmonary edema
- Aortic aneurysm/ dissection
- Digoxin toxicity
- Torsades de Pointes/ Ventricular fibrillation/ Atrial flutter/ Atrial Fibrillation
- Cardiac tamponade
- Ischemic Heart Disease/ Acute Myocardial Infarction

1. Cardiogenic shock

Causes:

- Hypovolemia: dehydration/ blood loss
- Septicemic shock: gram negative bacteria
- Drugs: rapid IV bolus injection of chloroquine, quinine; poisons
- Electrolyte abnormalities: hypo/ hypernatremia
- Hypoxemia
- Electricity
- Panic

Cont.

- Coronary artery disease
- Endocrine disorders: thyroid storm, Addisonian crisis
- Anaphylactic shock
- Vasovagal attack

Diagnosis

- P/E: absent pulse/ heart beat; Low or unrecordable BP (SBP < 90mmHg or has declined by > 30mmHg from previous level), cold clammy skin, cyanosis, altered sensorium
- Radiological
- Blood tests
- ECG/ Echo

Treatment

- Cardiac resuscitation
  - Airway (Position & ensure patency)
  - Breathing (re – establish breathing via ambu bag for e.g.)
  - Circulation (re – establish circulation via IV access)
  - Drugs
  - Examine
  - Follow up

Cardiac massage technique

- Place the patient on a firm bed.
- Use palms over the chest
- Use pressure with locked elbows
- 4 chest compressions alternating with 1 breath

Cont.

- Defibrillator 200 – 300 mcV
- IV **adrenaline** 1:10,000
- Minimum of 200mg IV **hydrocortisone** STAT
- At least 100ml of 50% **Dextrose** (or at least 50mls of 20% Dextrose)
- **Atropine** 0.6 – 2.4 mg in divided doses of 600mcg
- IVFs: dextrose, normal saline
- Treat the cause

2. Aortic dissection

- Relatively common, untreated fatal. Majority survive with treatment
- Commonest cause is **cystic medial necrosis commonly associated with Marfan's syndrome**. Other causes include HTN, pregnancy, coarctation or bicuspid aortic valve
- The 2nd MCC is arteriosclerosis

Cont.

- Commonest site of aortic dissection is:
  - ***Ascending aorta*** (2 – 5 cm above aortic valve) &
  - ***Descending aorta just distal to the origin of the left subclavian artery***.

Dissection of ascending aorta

- MC and most lethal.
- Most patients are under 60 yrs.
- Half have HTN

S/S

- S/S abrupt onset of severe chest pain
- Maximal at outset
- Most frequent at anterior chest, but may radiate or may be limited to inter – scapular area of the back
- There is a discrepancy between the carotid pulses, BP different in the 2 arms

Cont.

- If ***carotids*** are involved there is a sudden neurological deficit
- If the ***right coronary artery*** is involved there is brady – arrhythmias with or without signs of AMI
- In half there is ***acute aortic regurgitation***
- In severe cases there may be ***hemo – pericardium*** with rapid onset of tamponade

Diagnosis

- CXR: widened superior mediastinum, ascending aorta enlarged out of proportion to descending aorta
- Aortography

Treatment

- Surgical resection & grafting
- Drugs
  - Ganglion blockers: ***trimethaphan*** 0.3 – 3mg/ min infusion
  - ***Mecamylamine*** 2.5mg PO OD
  - Parenteral beta blockers: ***propranolol, metoprolol, esmolol, labetalol***
    - ***Labetalol***: can be given as a bolus of 50mg over 1 min repeated after 5 min PRN, max 200mg or infusion of 2mg/ min, range 50 – 200mg.

Cont.

- ***Propranolol***: 1mg over 1 min, can repeat after 2 min, PRN, max 10mg
- ***Metoprolol***: up to 5mg as 1 – 2 mg/ min, repeat after 5 min PRN, max. 10 – 15mg followed by PO 100 – 200mg/ d in 1 – 2 divided doses
- ***Esmolol:*** 50 – 200 mcg/kg/min infusion (short half life of about 8 min)

Cont.

- ***Sodium nitroprusside infusion*** – 0.5 – 1.5 mcg/kg/min. lower SBP to < 120mmHg
- ***Verapamil*** or ***diltiazem*** can be used if labetalol or nitroprusside can not used
- ***Aortic valve replacement*** if regurgitation is present

Complications

- Hemopericardium
- Hypotension
- Compromise of carotid or coronary arteries
- Aortic regurgitation
- Without treatment, death is due to rupture

Descending aortic dissection

- This is most likely to occur in ***elderly hypertensives***.
- Presents with sudden onset of chest pains, often inter – scapular, and often radiating to anterior chest.

Diagnosis

- ***CXR***: enlarged superior mediastinum, descending aorta may be larger than the ascending aorta
- ***Aortography*** is confirmatory
- Usually no need for urgent surgery: first control BP with drugs down to an SBP of 100 – 120mmHg.
- ***Trimethaphan*** or ***Na nitroprusside*** are the ideal first line drugs,

Cont.

- Propranolol or CCB should also be started orally.
- If pains are uncontrolled by drugs or there is evidence of disease progression by X ray or left pleural effusion → surgical correction should be done.
- If controlled by drugs: elective surgery should be done.

3. Digoxin toxicity

- Characterized by:
  - Nausea/ vomiting; Confusion; Color vision disturbance
  - Any arrhythmias could occur:
    - AF. Flutter
    - Atrial tachycardia
    - Ventricular tachycardia
    - Heart block
    - But the MC is ***type II heart block***

Cont.

- Diagnosis: confirmed by ***high digoxin levels > 2ng/mL***
- ***Treatment:***
  - Stop drug.
  - ***Digoxin antibodies***, Fab fragment 40mg stat
  - ***Phenytoin*** – 1 to 1.5 g IV BD or 500mg over 5 min, then every 5 min till reversed or toxic
  - ***Lignocaine*** 1 – 2% sol., 100mg IV LD, slowly over 1 – 2 mins, then tailor to response, half hourly

4. Cardiac arrhythmia

- Emergency situations:
  - V. tach.
  - V. fib.
  - Paroxysmal SVT
  - Atrial flutter
  - Atrial fibrillation
  - Wolff – Parkinson – White Syndrome
  - Torsades De Pointes

Cont.

- Arrhythmias are bad esp. when associated with:
  - Digoxin toxicity
  - MI
  - CCF
  - Endocarditis
  - Mural thrombus

SVT: Adenosine

- Drug of first choice.
- Short half life, 8 – 10s and side effects of short duration
- Half life prolonged after dipyridamole
- Unlike verapamil can be used after beta blockers. Verapamil is preferred in asthmatics
- Dose: rapid IV injection in central or large peripheral vein 3mg over 2s.

Cont.

- If necessary repeat 6mg after 1 – 2 minutes then 12 mg after a further 1 – 2 minutes. Don’t repeat if AV block occurs at any stage.
- Adverse effects;
  - Transient flush, chest pain, dyspnea, bronchospasm, choking sensation, nausea, light headedness, severe bradycardia.

Verapamil

- An initial slow IV dose of 5 – 10 mg over 2 minutes may be followed by oral treatment. Repeat IV dose of 5- 10 mg if necessary after 5 – 10 minutes. Under ECG monitor. Orally 80 – 120 mg TDS
- CI in:
  - AF with WPW syndrome
  - Children (unless specialist monitoring, and should not be combined with beta blockers)

Beta blockers

- IV beta blockers e.g. esmolol, propranolol, can achieve rapid control of ventricular rate
- Esmolol
  - For short term treatment of supraventricular arrhythmias including: ***AF***, ***atrial flutter***, ***sinus tachycardia***, ***tachycardia*** and ***HTN in peri – operative period***
- Dose IV infusion 50 – 200 mcg/kg/min

Adverse effects of esmolol

- Bradycardia
- Heart failure
- Heart block
- Hypotension
- Bronchospasm
- Peripheral vasoconstriction
- GIT disturbances
- Fatigue
- Sleep disturbances
- Rarely rashes, dry eyes, worsening of psoriasis

CI of esmolol

- Asthma, heart blocks, marked bradycardia, prinzmetal's angina, sick sinus syndrome, cardiogenic shock, metabolic acidosis, severe peripheral vascular disease, pheochromocytoma

Supraventricular & ventricular arrhythmias

- The following drugs are used:
  - Amiodarone
  - Beta blockers
  - Disopyramide
  - Flecainide
  - Propafenone,

Amiodarone

- Half life: 103 days
- Used in arrhythmias when other drugs are ineffective or CI.
- Indicated for:
  - Paroxysmal supraventricular, nodal & ventricular tachycardia
  - A. fibrillation & A. flutter
  - V. fibrillation
- Initiated only in hospital under specialist supervision
- Given PO or IV. IV dose can act very rapidly;

Cont.

- IV amiodarone is used in ***CPR for ventricular fibrillation or pulseless tachycardia*** unresponsive to other interventions.
- Dose: IV via central line, initially 5mg/kg over 20 – 120minutes with ECG monitoring. Can be repeated if necessary. Max 1.2g in 24 hours.
- Ventricular fibrillation or pulseless tachycardia by IV, 300mg over at least 3 minutes.

Cont.

- Has along half life of 103 days & takes many weeks or months to reach steady state concentrations
- ***Adverse effects:***
  - Corneal micro – deposits, photo – toxicity, hypo/hyperthyroidism, pneumonitis, peripheral neuropathy, hepatotoxicity.

Lidocaine

- For ventricular arrhythmias, especially after myocardial infarction.
- DOSE: IV 100mg bolus over a few minutes. 50 mg in smaller patients or in those with severely impaired circulation, followed by 4 mg/min for 30 minutes, then 2mg/min for 2 hours, then 1 mg/min. Reduce dose further if infusion goes on for over 24 hours.
- For injection: 2% lidocaine HCL, for infusion 0.1 or 0.2% in 5% dextrose infusion.

5. Pulmonary edema

- May be ***cardiogenic*** or ***non – cardiogenic***.
- To distinguish between the two:
  - Echocardiography (preferred)
  - PWCP catheter
- Causes are many & definitive management is aimed at treating the cause e.g. LVSD, MI, CCF
- Complications: infection, academia, anemia, renal failure (these should be corrected)

Management

- Sit up patient
- High flow 100% supplemental oxygen (consider NIPPV)
- ***Diuretics***
  - Lasix, initially 160 – 240 mg IV stat
- ***Morphine***: 2.4mg IV bolus or 10mg IM stat. can be repeated at least half an hr. later.

Cont.

- ***Nitrates***: nitroglycerine, isosorbide dinitrate
  - Nitroglycerin SL 0.4mg X 3 every 5 minutes for acute cardiogenic PE. If persists, infusion at 5 – 10mcg/min.
  - If hypertensive, Na nitroprusside 0.1 – 5 mcg/kg/min but requires close monitoring and arterial catheter in ICU.

Cont.

- ***ACEIs***
  - Reduce preload and afterload
  - Recommended in hypertensives. Use shot – acting drugs acutely
- Others: ***recombinant BNP (nesiritide)***

Cont.

- ***Vasodilator, diuretic***
  - Stat 2 mcg/kg IV bolus. Then 0.01 mcg/kg in an infusion
- In patients with severe LV dysfunction cardiogenic pulmonary edema, use sympathomimetic amines potent inotropes, biperidine phosphodiesterase inhibitors or cardiac glycosides

Cont.

- Sympathomimetic amines
- Dopamine 2-5mcg/kg/min initially then 5-10mcg/kg/min
- Dobutamine 2.5-10mcg/kg/min, adjust according to response
- Others dopexamine, isoprenaline, xamoterol
- Biperidine PE inhibitors- amrinone, milrinone
- Promote peripheral and pulmonary vasoldilation

Cont.

- Amrinone- 0.75mcg/kg stat, then 5-20mcg/kg/min infusion
- Milrinone 50mcg/kg stat, then 0.25-0.75mcg/kg/min
- Cardiac glycosides – To control ventricular rate in rapid atrial fibrillation or flutter and left ventricular dysfunction

6. Cardiac tamponade

- Pathophysiology: excessive pericardial effusion resulting in restrictive cardiomyopathy where ventricular function is impaired.
- Treatment is usually surgical.
- Most common cause is **TB pericarditis**
- Trauma is also a common cause

3. DRUGS FOR ISCHEMIC HEART DISEASE & HYPERLIPIDEMIA 29/1/2019

BY: DR. OCHANDA

Introduction

- The 3 leading causes of morbidity and mortality in ***developed*** countries is:
  - IHD
  - CVA
  - Cancer

Definitions

- ***Angina***: precordial chest pains referred to the left upper arm, shoulder or to the back; due to myocardial ischemia, worsened/ provoked by exertion, relieved by rest.
- ***Coronary Artery Disease*** encompasses both IHD & Myocardial infarction.

Spectrum of coronary arterial disease

- Types of angina in myocardial ischemia:
  - Stable or classic
  - Variant/ Prinzmetal angina → due to vasospasm worsened by atherosclerosis
  - Unstable angina → marked luminal narrowing (<10%)
- Worse states lead to myocardial infarction

Cont.

- The disease is due to narrowing of coronary vessels by atheromatous plaques, clots or vasospasm.
- When a large clot is finally formed in a narrow lumen, myocardial infarction occurs.

Management

- 1st line management is non – pharmacological
  - Reduce amount of cholesterol & highly saturated fats in the diet.
  - Reduce salt intake, treat HTN
  - Increase physical activity: vigorous exercise for ≥ half an hr. a day & ≥ 4 days in a week. The exercises should be vigorous enough to make you pant & sweat outdoors.
  - Stop smoking & drinking.

Pharmacological management

1. Nitrates & nitrites (***1st line***)
2. Thrombolytics
3. Anticoagulants
4. Anti – platelet agents
5. Anti – hyperlipidemia drugs
6. Other drugs: CCBs, Beta adrenergic blockers, ACEIs
7. Other treatments: surgery (CABG), thromboplasty (advancing a balloon catheter through the femoral artery into the heart)

Nitrates & Nitrites

- **Chemistry**: they are simple nitric & nitrous acid esters of poly alcohols. They are of 3 types:
  1. Very volatile liquids: amyl nitrite
  2. Moderately volatile liquids: nitroglycerin (prototype)
  3. Solids: isosorbide dinitrate
- They may loose potency due to volatilization & adsorption to plastic surfaces. Kept tightly closed in amber containers.

MoA

- They all release the nitrite ion NO_2^- that is further metabolized to NO in the vascular smooth muscle.
- The NO activates guanylyl cyclase in endothelial cells which then catalyzes the conversion of GTP → cyclic GMP.
- cGMP dephosphorylates myosin light chains resulting in relaxation.

Pharmacodynamics

- Nitroglycerin is denitrated in smooth muscle cells. The NO produced reacts with a sulfhydryl containing receptor on the enzyme guanylyl cyclase.
- Tolerance to nitrates occurs due ***to reduction in sulfhydryl groups and can be reversed by sulfhydryl regenerating agents***.
- PGE_2 and PGI_2 may also be involved in action
- Some compounds also have K^+ channel opening action besides NO activity.

Cont.

- Administration: PO, Inhalation, sublingual
- Classification:
  - Immediate acting: amyl nitrite & related nitrites (highly volatile liquids available in fragile glass ampules). Once absorbed they have a very short half life of 2 – 8 minutes.
    - Others: nitroglycerin (broken down into dinitroglycerin & mononitrate forms); immediate forms are either inhalational or sublingual; nitroglycerin can be given as continuous IV infusion
  - Intermediate acting
  - Long - acting

Cont.

- The drugs are selective & at therapeutic doses act almost exclusively on smooth muscles.
  - Vascular smooth muscles: relaxes both arterial & venular vessels. Action on arterioles and pre – capillary sphincters less than in larger vessels.
  - Venous capacitance is increased; Preload is decreased; Pulmonary vascular pressure and heart size are decreased; CO is reduced; Orthostatic hypotension is marked +/- syncope.
  - There is temporal artery pulsations and throbbing headaches; There's reflex tachycardia and myocontractility

Cont.

- Rapidly acting agents like ***amyl nitrite*** can cause reflex vasoconstriction due to excessive vasodilatation
- Coronary blood flow is increased in normal vessels. Relief of angina thought to be due to decreased preload and arterial pressure which decrease myocardial oxygen requirement.

Cont.

- Other smooth muscle organs:
  - SM of bronchi, GIT, biliary tract and genitourinary tract are relaxed, but briefly and clinically insignificant
  - Amyl nitrite and isobutyl nitrite have been used as sex enhancing drugs

Other effects

- Large doses of nitrites can cause pseudocyanosis, tissue hypoxia and death from formation of methemoglobin
- Sodium nitrite is used as a curing agent in meats
- If given soon after cyanide poisoning, can regenerate active cytochrome

Pharmacokinetics

- Oral bioavailability is only 10% due to rapid metabolism by a high capacity ***organic nitrate reductase*** in the liver. They are given sublingually to achieve therapeutic levels rapidly.
- Nitroglycerin and isosorbide dinitrate achieve therapeutic levels in minutes. Total duration of action is typically 15 – 30 minutes.

Cont.

- For longer duration of action, oral preps are used.
- Nitroglycerine is also given transdermally and by buccal route, using slow release preps.
- Amyl nitrite and related nitrites are highly volatile liquids, available in fragile glass ampoules in protective clothing which are crushed between fingers and inhaled.

Cont.

- The inhalation route is rapid and avoids first pass effect.
- Once absorbed unchanged nitrates have half lives of 2-8 minutes. Partially denitrated metabolites have half lives of up to 3 hours.
- Two metabolites of nitroglycerin, 2 dinitroglycerin and 2 mononitroglycerin forms have significant vasodilator action

Cont.

- The 5-mononitrate metabolite of isosorbide dinitrate is active and is available for clinical use as isosorbide mononitrate.
- Transdermal preps give nitroglycerine blood levels for 24 hrs, but hemodynamic effects last only 6-8 hrs.
- Excretion of denitrated metabolites in the form of glucoronide conjugates is largely through the kidneys.

Short acting:

- Nitroglycerin (SL) 0.15 – 1.2mg for 10 – 30 minutes (DoA)
- Isosorbide D (SL) 2.5 – 5 mg for 10 – 60 minutes.
- Amyl nitrite (inhalant) 0.18 – 0.3ml for 3 – 5 minutes.
- GTN IV continuous infusion 10 – 20 mcg/min

Long acting doses

- ***Nitroglycerin (oral, sublingual)*** 6.5 – 13mg for 6 – 8 hrs. (DoA)
- ***Nitroglycerin 2% (ointment)*** ½ to 2 inch 4hrly. For 3 – 6hrs.
- ***Nitroglycerin slow release (buccal)*** 1 – 2mg 4hrly for 3 – 6 hrs.
- ***Nitroglycerin slow release (dermal)*** 10 – 24 mg 24 hrly. For 8 – 10hrs.
- ***Isosorbide D (SL)*** 2.5 – 10mg 2hrly. For 1.5 – 2 hrs.

Cont.

- ***Isosorbide D (oral)*** 10 – 60mg 4 – 6 hrly. For 4 – 6 hrs.
- ***Isosorbide D (chewable)*** 5 – 10mg 2 – 4hrly. For 2 – 3 hrs.
- ***Pentaerythrytal tetranitrate*** 40 mg 6 – 8 hrly. For 6 – 8 hrs.
- ***Erythrytal tetranitrate*** 10 – 40 g 6 – 6 hrly. For 6 – 8 hrs.
- ***Nitrolingual spray, GTN*** 400mcg/MD, 1 – 2 doses SL for treatment & prophylaxis; For prophylaxis 1 – 2 doses under tongue, then close mouth as it is inflammable.
- ***Transiderm nitro patches*** 5’ -5mg/24hrs, 10’-10/24hrs, apply lateral chest wall (change sites), 1 per 24hrs.; change sites; Also used in CCF.

Cont.

- ***Isosorbide mononitrate***: initially 20mg 2 – 3 times / d PO then increase to 40 mg BD, max 120mg/d

Cont.

- Major acute toxicity: orthostatic hypotension, tachycardia, throbbing headache
- Dependence: in industrial workers manifests as variant angina. After 1 – 2 days away from exposure. Vasospasm may be serious enough to cause MI.
- Nitrosamines are powerful carcinogens, R2-N-NP. Associated with esophageal and gastric cancer/ also found in cigarette smoke.

THROMBOLYTICS

- Are the first drugs of choice once there is infarction.
- Tissue plasminogen activators are the most commonly used.
- After using thrombolytics, follow with heparin or the fractionated heparins.
  - For some fractionated heparins are better as they are also thrombolytic.
- Warfarin is then administered for long term.
- Antiplatelets may also be used (aspirin & clopidogrel)

CALCIUM CHANNEL BLOCKERS

- Voltage dependent L-type channels, characteristically large in conductance. Dominant in cardiac and smooth muscles. Receptors binds verapamil, diltiazem, and dihydropyridines. Are stereo selective. Decrease transmembrane calcium current associated with long lasting relaxation
- Receptor operated calcium channels are also reduced but not markedly.

Cont.

- T and N type channels are poorly sensitive to the blockades.
- Vascular SM are the most sensitive to calcium channel blockers. Arterials are more sensitive than veins.
- Effort angina reduced by reduction in peripheral resistance, reduction of coronary arteriole tone.

Cont.

- In myocardium – there is reduction in mechanical function reducing oxygen requirements, damaging effects of calcium influx prevented, reducing incidences of arrhythmias and ultimate infarct size, relieves or prevents coronary vasospasm.
- Diltiazem 75-150mcg/kg IV, 30-80 mg orally
- Verapamil 75-150mcg/kg IV, 80-160mg 8 hrly PO
- Nifedipine 3-10mcg/kg IV, 10-40mg 8hly orally

Cont.

- Inhibits smooth muscle contraction by blocking L – channels
  - Verapamil: 5mg IV stat in acute arrhythmias
  - Diltiazem (controls both arrhythmias & hypertension)
  - Dihydropiridines: used for long term management of CAD
    - Nifedipine
- Patients with IHD tend to present with arrhythmias esp. ventricular tachyarrhythmia
- CCBS are also coronary blood vessel vasodilators

Indications of CCB

- Angina treatment
- HTN
- SVT
- SAH: Nimodipine is used (is selective for cerebral blood vessels)

Beta blockers

- Benefits in angina is related to their hemodynamic effects on the cardiac workload by reducing the heart rate and myocontractility; they reduce the oxygen requirements at rest & at exercise. They reduce BP.
- They reduce the effects of ischemia. Low heart rate increases diastolic perfusion time that may increase myocardial perfusion.
- Any can be used but in the acute phase, a short acting beta blockers is preferred e.g. propranolol (to achieve the steady state concentrations rapidly); once the patient is stable, the patient can be placed on a longer acting beta blocker e.g. atenolol

Cont.

- Have an effect of causing redistribution to ischemic areas. They thus relieve angina and improve exercise tolerance.
- Undesirable effect is an increase in end diastolic volume, which increases myocardial oxygen requirement. Concomitant use with nitrates offsets this adverse effect.
- 3 effects in effort angina:

- Increase time to onset of angina, increase ST depression, decrease frequency and duration of episodes of silent myocardial ischemia in chronic stable angina

ACEIs

- Useful in MI in STEMI. Benefits additive to those of ASA and beta blockers.
- Benefit seen most in- elderly, anterior infarction, globally depressed LV function. Helpful for all hemodynamically stable patients with STEMI.
- Improves ventricular remodelling after MI with a subsequent reduction in risk of CHF.

- For long term maintenance therapy, long acting nitrates or CCB.
- In hypertensives, monotherapy with either CCB or Beta blockers may be adequate.
- Long acting nitrates preferred in normotensives.
- Combinations of beta blockers and CCB more effective.

- Nifedipine the preferred choice in those with persistent hypertension, sinus bradycardia, AV node dysfunction
- In heart failure nifedipine or diltiazem better tolerated
- In some cases all 3 types of drugs may be required
- Variant angina, nitrates and CCB preferred
- Unstable angina, verapamil more effective than beta blockers. Combination of nitrates, CCB nifedipine and a beta blocker most effective
- ASA is beneficial.
- Heparin and thrombolytic agents may be indicated.

- 1. Immediate treatment of angina, mostly sublingual nitroglycerin used.
- 2.IV nitroglycerin acts rapidly, but hemodynamic effects quickly reversed by stopping infusion. Use restricted to severe recurrent rest angina.
- 3. Slowly absorbed preps of nitroglycerin include a buccal form, an oral preparation and several transdermal preparations.
- They are used for prolonged treatment. Tolerance develops to them. This decreased by nitrate free periods, at least 8 hours in between doses.

Acute phase

- Thrombolytics
- Anticoagulants
- Antiplatelets

Maintenance (takes a minimum of 6 months)

- Long acting nitrates: isosorbide dinitrate (30mg 6 – 8hrly) or mononitrate (40mg OD)
- Variant angina: nitrates & CCB
- Unstable angina: verapamil
- Antihyperlipidemia drugs
- Rehabilitate the patient from the AMI by changing the diet, putting the patient under controlled exercise activity until they are stable.

ANTIHYPERLIPIDEMIA DRUGS

- HMG CoA Reductase Inhibitors: Lovastatin, Atorvastatin (20mg OD normally but after CAD place on 40 mg BD for up to 6 months), Fluvastain, Pravastatin, Simvastatin, Rosuvastatin (5mg OD)
- Most effective in reducing LDL
- Also have anti – inflammatory & healing properties on damaged myocardial tissue
- A/E: myalgia (stop asap; rosuvastatin has the least propensity to cause myalgia)

Nicotinic acid

- Reduces both LDL & VLDL
- Often increases HDL (protective against atherosclerosis)
- Decreases VLDL secretion → reducing LDL production & blood levels
- A/E: headache; rebound effect

Fibric acid derivatices

- Include: gemfibrozil, fenofibrate, bezafibrate
- Decrease VLDL and in some LDL; also tend tto decrease TGs

Bile acid binders

- Colestipol, cholestyramine, colesevelum
- Prevent cholesterol absorption
- Used in combination with nicotinic acid or with HMG CoA reductase inhibitors

Inhibitors of intestinal sterol absorption: ezetimibe

- Reduce cholesterol & phytosterol not absorbed
- A/E: bloating, flatus, malabsorption, deficiency of fat soluble vitamins

Newer drugs

- Nicorandil-K channel inhibitor, vasodilates CA, decreases both preload and afterload
- Ranolazine-pFOX inhibitors, blockage of late Na currents which facilitate ca entry.
- Ivabradine –selective I_i Na channel blocker, in the SA node, reducing heart rate. As effective as CCB and Beta blockers.

4. MANAGEMENT OF CCF

TYPED BY NAILA KAMADI

Definition

- **Heart failure** is a progressive clinical syndrome characterized by the inability of the heart to maintain adequate cardiac output to meet the body's metabolic needs either due to *an abnormality in structure* or *at the expense of high filling pressures*.

Causes of heart failure

- ↓ ***ventricular contractility (EF < 40%):*** MI, Myocarditis, Cardiomyopathy
- ***Ventricular outflow obstruction:*** HTN, AS, PAH, PS
- ***Ventricular inflow obstruction:*** MS, TS
- ***Ventricular volume overload:*** VSD, VSD. Increased metabolic demand
- ***Arrhythmia:*** Atrial fibrillation, Complete heart block
- ***Diastolic dysfunction:*** constrictive pericarditis, RCM, cardiac tamponade

Pathophysiology

- ↓ CO → activation of counter – regulatory neuro hormonal mechanisms:
  - RAAS → vasoconstriction, salt & water retention & SNS activation
  - Endothelin – 1
  - Natriuretic peptides
  - ADH

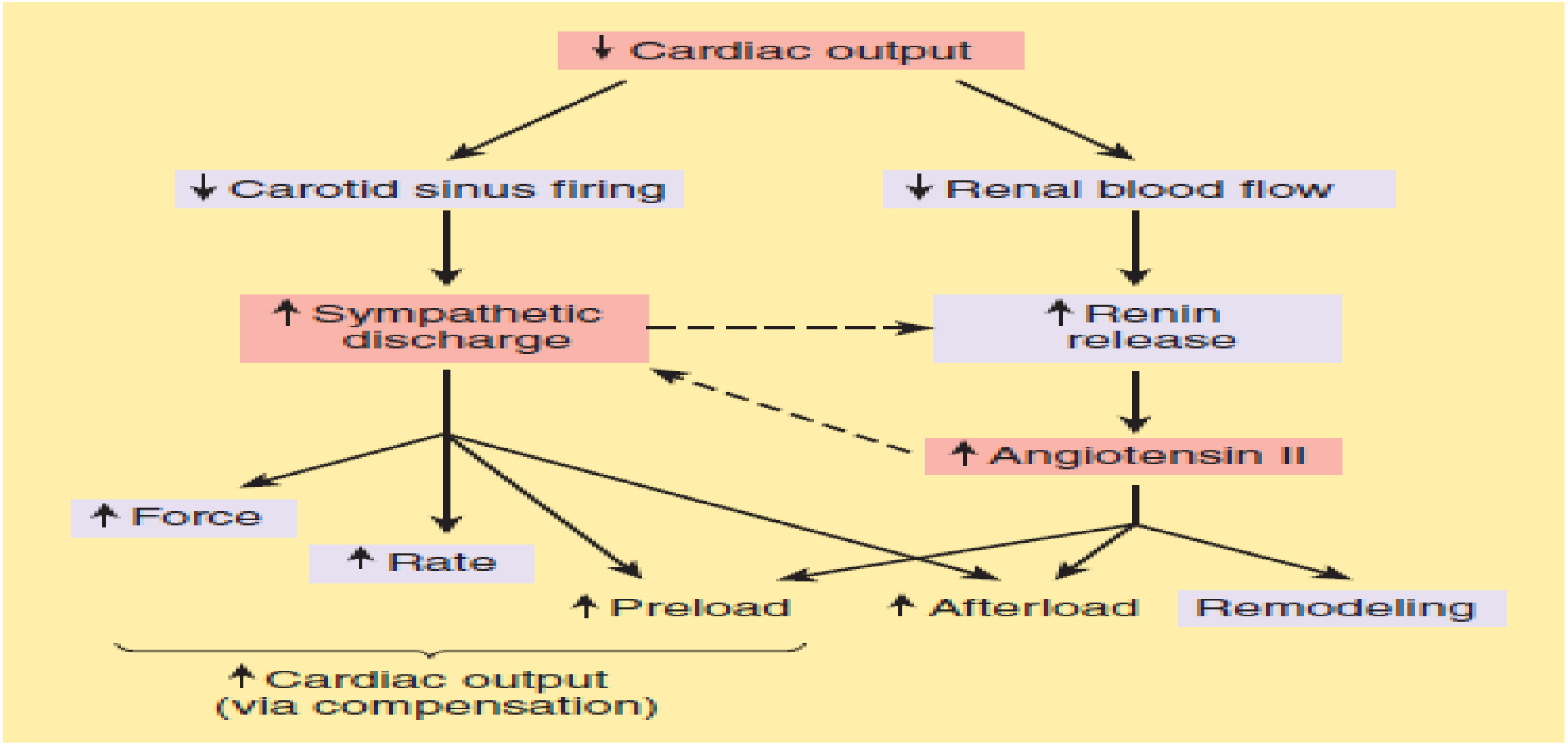


FIGURE 13–2 Some compensatory responses that occur during congestive heart failure. In addition to the effects shown, sympathetic discharge facilitates renin release, and angiotensin II increases norepinephrine release by sympathetic nerve endings (*dashed arrows*).

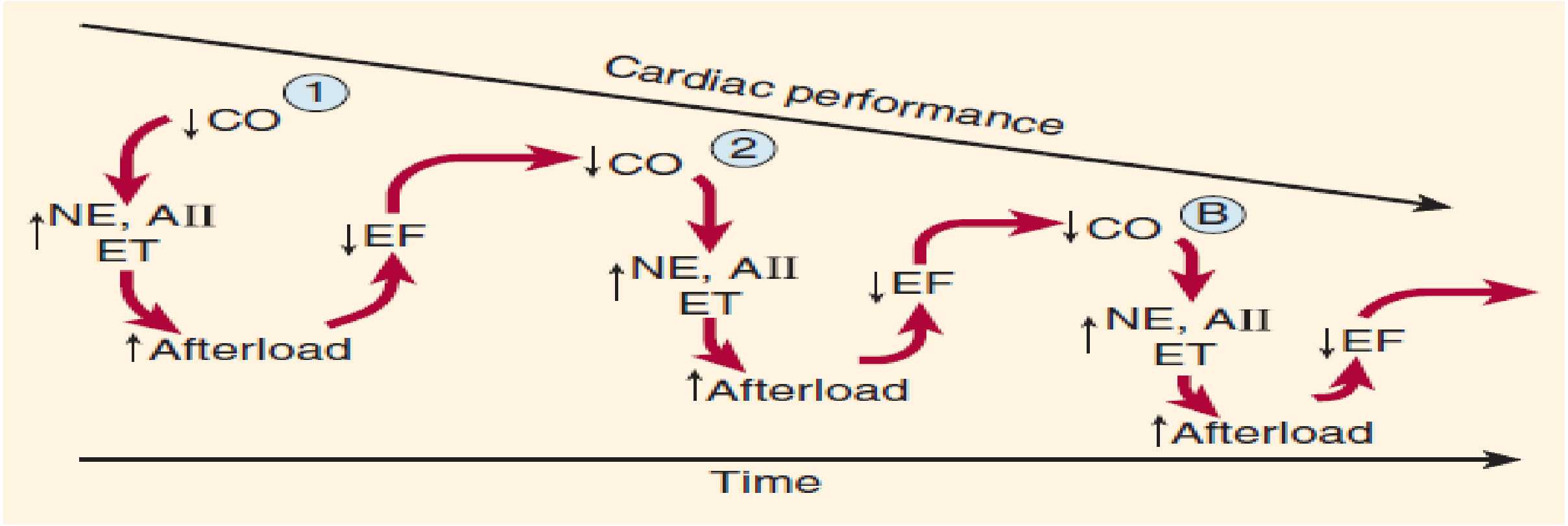


FIGURE 13–3 Vicious spiral of progression of heart failure. Decreased cardiac output (CO) activates production of neurohormones (NE, norepinephrine; AII, angiotensin II; ET, endothelin), which cause vasoconstriction and increased afterload. This further reduces ejection fraction (EF) and CO, and the cycle repeats. The downward spiral is continued until a new steady state is reached in which CO is lower and afterload is higher than is optimal for normal activity. Circled points 1, 2, and B represent points on the ventricular function curves depicted in Figure 13–4.

Classification

Anatomical classification

- ***Left Heart Failure***:↓ LV output → ↑ LA pressure → pulmonary edema acutely& pulmonary HTN chronically.
- ***RHF***: ↓ RV output → systemic venous congestion.
- ***Biventricular Heart Failure***.

Cont.

Based on Ejection Fraction (*Normal EF is >60%*)

- Heart Failure with Reduced Ejection Fraction (HFrEF) → systolic dysfunction with EF < 40%.
- Heart Failure with Preserved Ejection Fraction (HFpEF) → diastolic dysfunction with EF >40% (stiffening & loss of adequate relaxation of LV resulting in reduced filling & CO)
- Heart Failure with Mid – Range Ejection Fraction (HFmEF).

Cont.

Based on duration of symptoms

- Acute heart failure
- Chronic heart failure
- Acute on chronic heart failure

High output heart failure

- Demands of the body are so great that increased CO is insufficient.
- Causes:
  - Hyperthyroidism
  - Anemia
  - Arteriovenous shunts
  - Beriberi
- Rx the underlying cause.

TACC/AHA Stages of HF		NYHA Functional Classification	
A	No objective evidence of cardiovascular disease (CVD). No symptoms and no limitation in ordinary physical activity.	None	
B	Objective evidence of ***minimal*** CVD. ***Mild*** symptoms & slight limitation during ordinary activity. Comfortable at rest.	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
C	Objective evidence of ***moderately severe*** CVD. ***Marked*** limitation in activity due to symptoms even, during less – than – ordinary activity. Comfortable at rest.	II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.
		III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.
D	Objective evidence of ***severe*** CVD. ***Severe*** limitation in activity.	IV	Unable to carry on any physical activity without symptoms of HF, or symptoms

Signs & symptoms

Symptoms

- ***Typical***: Breathlessness, orthopnea PND, ↓ exercise tolerance *(major direct consequence of ↓ CO)*, fatigue, ankle swelling
- ***Less typical***: nocturnal cough, wheezing, bloated feeling, bendopnea, anorexia, confusion (esp. in the elderly), palpitations, dizziness, syncope.

Cont.

Signs

- ***Specific***: Elevated JVP, Hepatojugular reflex, 3rd heart sound (gallop rhythm), lateral displaced apical impulse
- ***Less specific***: Weight gain (>2kg/week), cardiac murmurs, tachycardia, irregular pulse, narrow pulse pressure, peripheral edema, pulmonary crackles, dullness on percussion at lung bases (pleural effusion), tachypnea, Cheyne Stokes respiration (late), Hepatomegaly/ ascites, cold extremities, oliguria,.

Treatment goals

1. Reducing symptoms
2. Slowing progression during relatively stable periods
3. Managing acute episodes of decompensated failure

TABLE 13–1 Drug groups used in heart failure.

Chronic heart failure	Acute heart failure
Diuretics	Diuretics
Aldosterone receptor antagonists	Vasodilators
Angiotensin-converting enzyme inhibitors	Beta agonists
Angiotensin receptor blockers	Bipyridines
Beta blockers	Natriuretic peptide
Cardiac glycosides	
Vasodilators	

Cont.

Positive inotropes:

- Cardiac glycosides
- Bipyridines
- β agonists

Drugs without positive inotropic effect:

- Diuretics
- RAAS inhibitors
- Vasodilators
- β blockers

Cardiac glycosides/ cardenolides

- Include: ***digoxin, digitoxin***
- MoA: inhibits Na^+/K^+ - ATPase → ↑ intracellular Na^+ → ↓ Ca^{2+} expulsion from cell by the Na^+ - Ca^{2+} exchanger → ↑ intracellular Ca^{2+} → positive inotropy

TABLE 13–2 Effects of digoxin on electrical properties of cardiac tissues.

Tissue or Variable	Effects at Therapeutic Dosage	Effects at Toxic Dosage
Sinus node	↓ Rate	↓ Rate
Atrial muscle	↓ Refractory period	↓ Refractory period, arrhythmias
Atrioventricular node	↓ Conduction velocity, ↑ refractory period	↓ Refractory period, arrhythmias
Purkinje system, ventricular muscle	Slight ↓ refractory period	Extrasystoles, tachycardia, fibrillation
Electrocardiogram	↑ PR interval, ↓ QT interval	Tachycardia, fibrillation, arrest at extremely high dosage

Effects of digitalis on other organs

- NB: ***cardiac glycosides affect all excitable tissues***
- GIT (MC extra – cardiac site of digitalis toxicity): nausea, vomiting, diarrhea
- CNS: disorientation, hallucinations, visual disturbances (aberrations of color perception)
- Gynecomastia

Digitalis & other electrolytes

Potassium

- Digitalis & Potassium inhibit each other's binding to the Na^+/K^+ - ATPase
  - Hyperkalemia reduces enzyme inhibiting actions of cardiac glycosides
  - Hypokalemia facilitates this actions.
- Abnormal cardiac automaticity is inhibited by hyperkalemia, i.e., hyperkalemia reduces toxic effects of digitalis.

Cont.

Calcium

- Ca^{2+} facilitates toxic actions of cardiac glycosides by accelerating the overloading of intracellular Ca^{2+} stores
- Hypercalcemia increases risk of digitalis – induced arrhythmia

Magnesium: opposite to Ca^{2+}

These interactions mandate careful evaluation of serum electrolytes in patients with digitalis – induced arrhythmias!

Bipyridines

- Include: inamrinone, Milrinone
- MoA: inhibit PDE – 3 → ↑ cAMP →
  - ↑ myocardial contractility by ↑ inward Ca^{2+} flux
  - Vasodilating effect
- A/E
  - Inamrinone: nausea, vomiting, arrhythmias, thrombocytopenia, liver enzyme changes
  - Milrinone: arrhythmias
- Only used IV and only for acute HF or severe exacerbation of chronic HF.

β agonists

- ***Dobutamine***, a selective β_1 agonists have been most widely used. ***Dopamine*** has also been used in acute HF & may be helpful if there is need to raise BP.
- MoA:
  - ↑ CO & ↓ ventricular filling pressure.
- Disadvantages:
  - Some tachycardia & ↑ myocardial oxygen consumption has been reported hence there is a potential for producing ***angina*** or ***arrhythmias*** in patients with coronary artery disease.
  - Tachyphylaxis may occur

Diuretics

- Include: ***Frusemide***; Aldosterone antagonist diuretics (PSDs): ***spironolactone, eplerenone***
- Drugs of choice in HF
- MoA:
  - ↓ venous pressure & ventricular preload → ↓ salt & water retention & edema & its symptoms
  - PSDs also decrease morbidity & mortality in patients with severe heart failure who are also receiving ACEIs.
    - Possible mechanism: aldosterone may also cause myocardial & vascular fibrosis and baroreceptor dysfunction in addition to its renal effects.

RAAS Antagonists

- **ACEI e.g. captopril**
  - ↓ afterload,
  - ↓ Salt & water retention (by ↓ aldosterone secretion)
  - ↓ preload
  - ↓ sympathetic activity (by diminution of angiotensin's presynaptic effects on norepinephrine release)
  - ↓ long term remodeling of heart & vessels hence ↓ mortality & morbidity

Cont.

- **ARBs e.g. Losartan**
  - Similar but more limited beneficial effects as ACEIs
  - Consider in patients intolerant to ACEIs because of incessant cough.
  - In some trials, ***candesartan*** was beneficial when added to an ACEI.
- **Aliskiren (renin inhibitor):** approved for HTN but still in trials for HF.

Vasodilators

- In acute HF, they produce a ↓ in preload (through venodilation) or a ↓ in afterload (through arteriolar dilation) or both.
- Some evidence suggests that long term use of ***hydralazine*** & ***isosorbide dinitrate*** can also reduce damaging remodeling of heart.
- ***Nesiritide*** (synthetic BNP) is approved for use in acute HF. It ↑ **cGMP in smooth muscles & ↓ venous & arteriolar tone** in experimental preparations. It also causes ***diuresis***.
  - Short half life of 18 minutes
  - Administered as a bolus IV dose followed by continuous infusion
  - Most common A/E: hypotension

Cont.

- NB: plasms concentrations of endogenous BNP rise in most patients with HF & are correlated with severity. Measurement of plasma BNP has become a useful diagnostic or prognostic test in some centers.
- Related peptides:
  - Atrial natriuretic peptide: carperitide is the synthetic analog
  - Urodilatin: ularitide is the synthetic analogue.
- Orally active competitive inhibitors of endothelin:
  - Bosentan (*approved for use in pulmonary HTN but has significant teratogenic & hepatotoxic effects*)
  - Tezosentan

β blockers

- Include: bisoprolol, carvedilol, metoprolol, nebivolol
- Used in chronic HF
- MoA:
  - Attenuation of adverse effects of high concentrations of catecholamines (including apoptosis)
  - Up regulation of β receptors
  - ↓ heart rate
  - ↓ remodeling through inhibition of mitogenic activity of catecholamines

Acute heart failure

- Precipitants of acute on chronic HF
  - ***F***orgot medication: lack of compliance, inadequate dosage, inappropriate medication
  - ***A***rrhythmias e.g. Atrial Fibrillation
  - ***I***schemia, ***I***nfarction, Intercurrent ***I***nfection
  - ***L***ifestyle: increased exertion, emotion, excess salt intake
  - ***U***p regulation states: metabolic needs (pregnancy, thyrotoxicosis, anemia, fever), IVF overload
  - ***R***enal failure
  - ***E***mbolism

Management of acute HF

Supportive

- Sit up patient in semi – recumbent position.
- High flow 100% O_2 if SpO_2 is < 90%.
- Monitor: BP, ECG, SpO_2
- Strict bed rest.

Cont.

Definitive: Gain IV (gut wall edema limits absorption of oral medications) access & start:

- Diuresis to reduce congestion: ***Frusemide***, ***Metolazone*** (in frusemide resistance to augment diuresis)
  - ***Exercise caution! Monitor hydration status, I/O & U/E/Cr to avoid AKI &/or electrolyte imbalances***
- Venodilation to relieve pulmonary congestion: ***GTN***, nitroprusside, nesiritide
- Positive inotropy for *severe, protracted hypotension*: ***Dobutamine*** or ***dopamine***
- Vasopressin antagonist for euvolemic hyponatremia: ***conivaptan***
- ***Diamorphine*** 1.25 – 5mg IV slowly when in extremis

Management of chronic HF

- Lifestyle modification: education, low – salt diet, smoke & alcohol cessation, regular moderate aerobic exercise
- Influenza & pneumococcal vaccination
- Glycemic control in DM
- BP optimization in HTN
- Statin therapy in hyperlipidemia

Drug therapy in symptomatic chronic HF

- Principles:
  - Optimize preload if congested.
  - ↑ contractility & ↓ afterload if CO is ↓.

Sodium removal

- Dietary salt restriction & diuretic if edema is present.
- Mild HF: thiazide; more severe forms: frusemide
- Rx of resultant hypokalemia: supplementation, use PSD or ACEI
  - NB: ***spironolactone*** & ***eplerenone*** appear to reduce morbidity & mortality hence consider in all patients with moderate – severe HF.

Cont.

ACEIs & ARBs

- Drug of choice in LV dysfunction but no edema.
- First line therapy in chronic HF: ACEIs & diuretics
- Patients withdrawn from digoxin deteriorate while on ACEIs
- ARBs are reserved for patients who cannot tolerate ACEIs.

Cont.

Vasodilators

- If high filling pressures with dyspnea due to pulmonary congestion: venodilators preferred, i.e., ***long acting nitrates***
- If low LV output with fatigue: arteriolar dilator preferred, i.e., ***hydralazine***
- If both issues are present: dilation of both arterioles & veins is required hence combination therapy is used, i.e., isosorbide dinitrate & hydralazine (***BiDil***)

Cont.

***β* – blockers**

- ***Bisoprolol, Carvedilol, Metoprolol & Nebivolol*** have been shown to reduce mortality.
- MoA: inhibiting excessive tachycardia & adverse effects of catecholamines
- Use with caution at low doses
- Improvement is noted with several months of therapy & includes: slight ↑ in EF, slower HR, ↓ in symptoms.

Cont.

Ivabradine

- Alternative to beta blocker therapy:
- An I_f blocker
- Can slow heart rate in *HF patients with stable symptomatic chronic heart failure* in *sinus rhythm* & on *maximally tolerated doses of beta blockers* or have a *contraindication to beta blocker use*.

Cont.

Digitoxin

- Indication: HF with atrial fibrillation
- Only administered when diuretics & ACEIs have failed to control symptoms.
- Mild symptoms: slow loading (digitalization) is safer.
- Has moderate but persistent positive inotropic effect.
- Reduces hospitalization & deaths from progressive heart failure at the expense of an increased risk of sudden death.

Cont.

- Managing digitalis toxicity:
  - Visual changes & GIT disturbances: reduce dose
  - Cardiac arrhythmias: monitor digitalis levels, potassium (avoid hypokalemia esp. in patients on dialysis) & ECG
  - Severe toxicity:
    - Cardiac pacemaker catheter
    - Administer digitalis antibodies (digoxin immune fab)
    - Reserve cardioversion only for glycoside induced ventricular fibrillation

SUMMARY Drugs Used in Heart Failure

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
DIURETICS				
• Furosemide	Loop diuretic: Decreases NaCl and KCl reabsorption in thick ascending limb of the loop of Henle in the nephron (see Chapter 15)	Increased excretion of salt and water • reduces cardiac preload and afterload • reduces pulmonary and peripheral edema	Acute and chronic heart failure • severe hypertension • edematous conditions	Oral and IV • duration 2–4 h • *Toxicity:* Hypovolemia, hypokalemia, orthostatic hypotension, ototoxicity, sulfonamide allergy
• Hydrochlorothiazide	Decreases NaCl reabsorption in the distal convoluted tubule	Same as furosemide, but less efficacious	Mild chronic failure • mild-moderate hypertension • hypercalciuria • has not been shown to reduce mortality	Oral only • duration 10–12 h • *Toxicity:* Hyponatremia, hypokalemia, hyperglycemia, hyperuricemia, hyperlipidemia, sulfonamide allergy
• *Three other loop diuretics: Bumetanide and torsemide similar to furosemide; ethacrynic acid not a sulfonamide*				
• *Many other thiazides: All basically similar to hydrochlorothiazide, differing only in pharmacokinetics*				
ALDOSTERONE ANTAGONISTS				
• Spironolactone	Blocks cytoplasmic aldosterone receptors in collecting tubules of nephron • possible membrane effect	Increased salt and water excretion • reduces remodeling • reduces mortality	Chronic heart failure • aldosteronism (cirrhosis, adrenal tumor) • hypertension • has been shown to reduce mortality	Oral • duration 24–72 h (slow onset and offset) • *Toxicity:* Hyperkalemia, antiandrogen actions
• *Eplerenone: Similar to spironolactone; more selective antialdosterone effect; no significant antiandrogen action; has been shown to reduce mortality*				

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
ANGIOTENSIN ANTAGONISTS				
Angiotensin-converting enzyme (ACE) inhibitors: • Captopril	Inhibits ACE • reduces AII formation by inhibiting conversion of AI to AII	Arteriolar and venous dilation • reduces aldosterone secretion • reduces cardiac remodeling	Chronic heart failure • hypertension • diabetic renal disease • has been shown to reduce mortality	Oral • half-life 2–4 h but given in large doses so duration 12–24 h • *Toxicity:* Cough, hyperkalemia, angioneurotic edema • *Interactions:* Additive with other angiotensin antagonists
Angiotensin receptor blockers (ARBs): • Losartan	Antagonize AII effects at AT_1 receptors	Like ACE inhibitors	Like ACE inhibitors • used in patients intolerant to ACE inhibitors • has been shown to reduce mortality	Oral • duration 6–8 h • *Toxicity:* Hyperkalemia; angioneurotic edema • *Interactions:* Additive with other angiotensin antagonists
• *Enalapril, many other ACE inhibitors: Like captopril*				
• *Candesartan, many other ARBs: Like losartan*				
BETA BLOCKERS				
• Carvedilol	Competitively blocks β_1 receptors (see Chapter 10)	Slows heart rate • reduces blood pressure • poorly understood effects • reduces heart failure mortality	Chronic heart failure: To slow progression • reduce mortality in moderate and severe heart failure • many other indications in Chapter 10	Oral • duration 10–12 h • *Toxicity:* Bronchospasm, bradycardia, atrioventricular block, acute cardiac decompensation • see Chapter 10 for other toxicities and interactions
• *Metoprolol, bisoprolol, nebivolol: Select group of β blockers that have been shown to reduce heart failure mortality*				

CARDIAC GLYCOSIDE				
• Digoxin	Na^+/K^+-ATPase inhibition results in reduced Ca^{2+} expulsion and increased Ca^{2+} stored in sarcoplasmic reticulum	Increases cardiac contractility • cardiac parasympathomimetic effect (slowed sinus heart rate, slowed atrioventricular conduction)	Chronic symptomatic heart failure • rapid ventricular rate in atrial fibrillation • has not been definitively shown to reduce mortality	Oral, parenteral • duration 36–40 h • *Toxicity:* Nausea, vomiting, diarrhea • cardiac arrhythmias
VASODILATORS				
Venodilators:				
• Isosorbide dinitrate	Releases nitric oxide (NO) • activates guanylyl cyclase (see Chapter 12)	Venodilation • reduces preload and ventricular stretch	Acute and chronic heart failure • angina	Oral • 4–6 h duration • *Toxicity:* Postural hypotension, tachycardia, headache • *Interactions:* Additive with other vasodilators and synergistic with phosphodiesterase type 5 inhibitors
Arteriolar dilators:				
• Hydralazine	Probably increases NO synthesis in endothelium (see Chapter 11)	Reduces blood pressure and afterload • results in increased cardiac output	Hydralazine plus nitrates have reduced mortality	Oral • 8–12 h duration • *Toxicity:* Tachycardia, fluid retention, lupus-like syndrome
Combined arteriolar and venodilator:				
• Nitroprusside	Releases NO spontaneously • activates guanylyl cyclase	Marked vasodilation • reduces preload and afterload	Acute cardiac decompensation • hypertensive emergencies (malignant hypertension)	IV only • duration 1–2 min • *Toxicity:* Excessive hypotension, thiocyanate and cyanide toxicity • *Interactions:* Additive with other vasodilators

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
BETA-ADRENOCEPTOR AGONISTS				
• Dobutamine	$Beta_1$-selective agonist • increases cAMP synthesis	Increases cardiac contractility, output	Acute decompensated heart failure • intermittent therapy in chronic failure reduces symptoms	IV only • duration a few minutes • *Toxicity:* Arrhythmias • *Interactions:* Additive with other sympathomimetics
• Dopamine	Dopamine receptor agonist • higher doses activate β and α adrenoceptors	Increases renal blood flow • higher doses increase cardiac force and blood pressure	Acute decompensated heart failure • shock	IV only • duration a few minutes • *Toxicity:* Arrhythmias • *Interactions:* Additive with sympathomimetics
BIPYRIDINES				
• Inamrinone, milrinone	Phosphodiesterase type 3 inhibitors • decrease cAMP breakdown	Vasodilators; lower peripheral vascular resistance • also increase cardiac contractility	Acute decompensated heart failure • increase mortality in chronic failure	IV only • duration 3–6 h • *Toxicity:* Arrhythmias • *Interactions:* Additive with other arrhythmogenic agents
NATRIURETIC PEPTIDE				
• Nesiritide	Activates BNP receptors, increases cGMP	Vasodilation • diuresis	Acute decompensated failure • has not been shown to reduce mortality	IV only • duration 18 minutes • *Toxicity:* Renal damage, hypotension, may increase mortality

5. ACTIONS & USES OF THROMBOLYTIC AGENTS

15/1/2019

BY: DR. M. EZZI

Definition

- Thrombolytics are used to lyse already formed blood clots as ischemia may be fatal.
- These drugs are mostly used in **very acute settings**.

Goal of thrombolytic therapy

- Rapid restoration of blood flow in an occluded vessel
- Accelerated proteolysis of thrombus
- Part of an overall anti – thrombotic plan:
  - Anticoagulants
  - Anti – platelet agents
  - Mechanical approaches

Indications of thrombolytics

- **Acute STEMI**: if the patient presents within 3 – 4 hrs.
- **Acute ischemic stroke**: in patients that present within the 1st 6 hrs. of the symptoms of a stroke. ***ENSURE THE STROKE IS NOT HEMORRHAGIC***.
- **PTE**: for massive embolism that causes hemodynamic instability e.g. saddle thromboembolism
- Peripheral artery occlusion
- DVT

Rationale in AMI

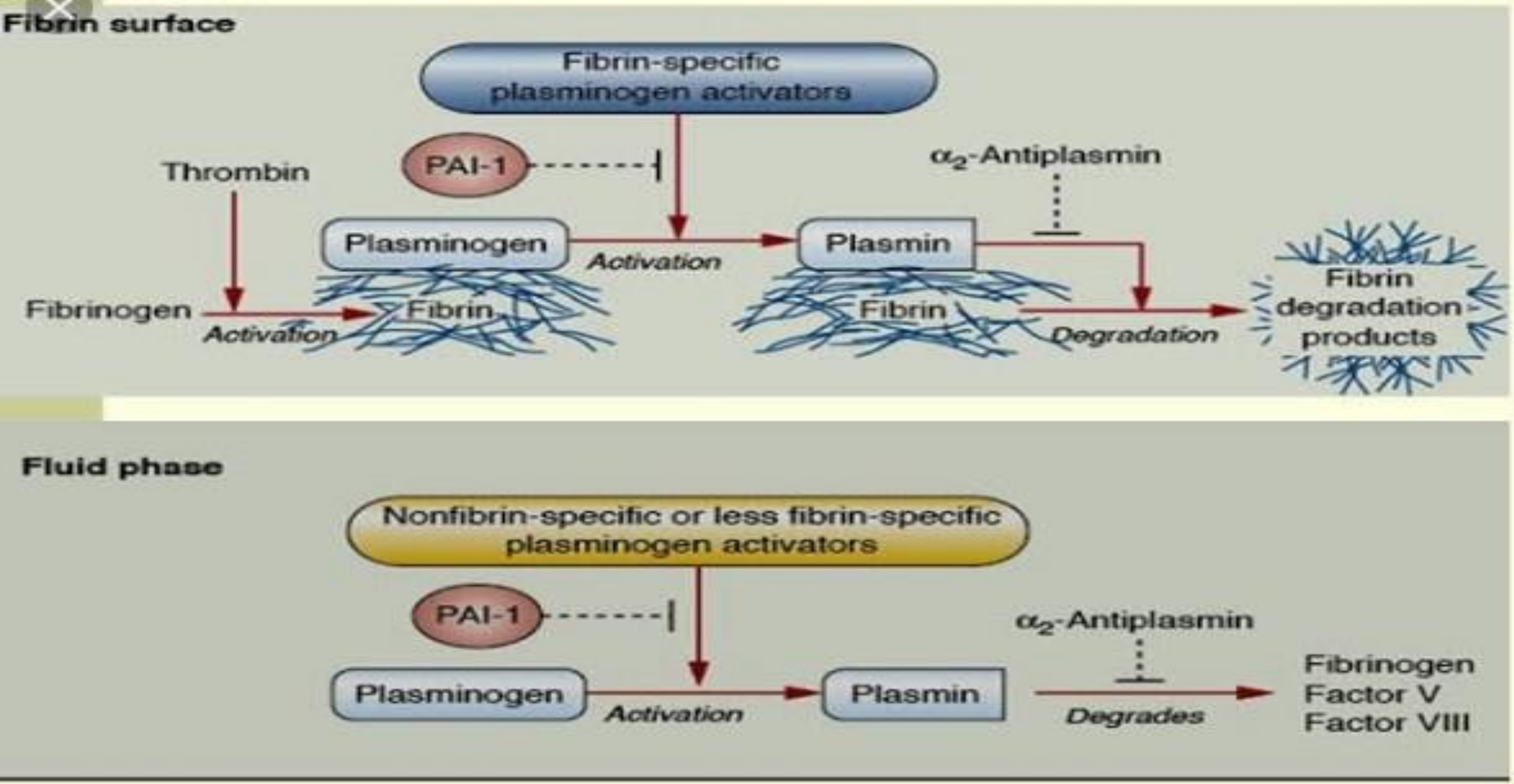
- Thrombolytics should be given immediately & they are used to:
  - Improve ventricular function
  - Reduce incidence of CHF
  - Reduce mortality

Mechanism of action

- Stimulation of **plasminogen activation**.
- Mediate conversion of **plasminogen** (proenzyme) to **plasmin** (active enzyme)
  - Plasmin is a non – specific protease that breaks down fibrin, fibrinogen, factor V & factor VIII to soluble degradation products
- Lysis of the insoluble fibrin clot into soluble derivatives.

Classification of thrombolytics

1. Non – fibrin specific
   - Streptokinase
   - Urokinase
   - Anistreplase
2. Fibrin specific (Tissue Plasminogen Activators, t – PA)
   - Alteplase
   - Reteplase
   - Tenecteplase



PAI= plasminogen activator inhibitor

Non – fibrin specific

- Binds equally to both circulating & non circulating plasminogen
- Produces breakdown of clot (local fibrinolysis) and circulating plasminogen (systemic fibrinolysis)
- Systemic fibrinolysis increases the chances of systemic bleeding

Fibrin – specific (t – PA)

- Selective in action (clot or fibrin specific)
- Binds preferentially to plasminogen at the fibrin surface (non – circulating) rather than circulating plasminogen in blood
- Risk of bleeding is less
- Activity is enhanced upon binding to fibrin

Streptokinase

- Bacterial protein produced by **beta hemolytic streptococci**
- Acts indirectly by binding to plasminogen & forming a plasminogen – streptokinase complex, i.e., activator complex
- The complex converts inactive plasminogen to active plasmin

PK

- Half life of 20 mins
- Give as IV infusion
  - Bolus of 250000U
  - 100000 U/h for 24 – 72h
- Least expensive thrombolytic
- Used for both venous or arterial thrombosis

A/E

- Antigenicity
  - High titer antibodies develop 1 to 2 weeks after use
  - Precluding retreatment until titer declines
- Allergic reaction: rashes, fever, hypotension
- Bleeding due to systemic fibrinolysis: can range from GI to intracranial bleeds

Precautions

- Recent streptococcal infection
- Previous administration of the drug
- Develop allergic reactions, resistance due to antistreptococcal antibodies

Anistreplase (APSAC)
anisoylated plasminogen streptokinase activator complex

- Is acylated plasminogen combined with streptokinase
- Prodrug – deacylated in circulation into active plasminogen – streptokinase complex
- Half life is 70 – 120 min

Overview

- Given as a bolus IV injection (30U over 3 – 5 min)
- Longer DOA
- More thrombolytic activity
- Greater clot selectivity
- Similar A/E to streptokinase but occur less
- More expensive than streptokinase

Urokinase

- Human enzyme synthesized by the kidney
- Obtained from urine or cultures of human embryonic kidney cells
- Direct plasminogen activator
- Given by IV infusion
  - Bolus of 30000U over 10 min
  - 300000U/h for 12h

Overview

- Half life of about 12 – 20 minutes
- Lyses of acute massive PTE
- No anaphylaxis – not antigenic
- Minimal fibrin specificity
- Associated with systemic lysis
- Expensive hence use is limited

T – PA

- Prepared by recombinant DNA technology
- Include:
  - Alteplase
  - Reteplase
  - Tenecteplase

MoA

- Activate fibrin bound plasminogen rather than free plasminogen in blood → reduces systemic lysis
- Action enhanced by presence of fibrin
- Binds to fibrin and converts entrapped plasminogen to plasmin
- Followed by activated local fibrinolysis with limited systemic fibrinolysis

Advantages

- Fibrin specific drugs are clot specific
- Limited systemic fibrinolysis – reduced risk of bleeding
- Not antigenic hence can be used in patients with prior anti – streptococcal antibodies

Alteplase

- Very short half life of about 5 min
- Administered IV
  - 60mg bolus
  - 40mg infusion over 2h

Reteplase

- Longer duration than Alteplase (15 min)
- Enhanced fibrin specificity
- Given as 2 IV bolus injections of 10U each

Tenecteplase

- Half life of 30 minutes.
- Administered as a single IV bolus.
- Most fibrin – specific of all the t – Pas.
- Only approved in acute MI.

Contraindications: to prevent the patient from systemic bleeding

Absolute contraindications:

- Prior intracranial hemorrhage.
- Known structural cerebral vascular lesions e.g. AVM
- Known malignant intracranial neoplasm.
- Ischemic stroke within 3 months.
- Suspected aortic dissection.

Cont.

- Active bleeding or bleeding diathesis (excluding menses).
- Significant closed head trauma or facial trauma within 3 months.
- Intracranial or intraspinal surgery within 2 months.
- Severe uncontrolled HTN unresponsive to emergency therapy.
- For ***streptokinase***, prior treatment within the previous 6 months

Cont.

Relative contraindications:

- History of chronic, severe, poorly controlled HTN
- Significant HTN on presentation (SBP > 180mmHg or DBP > 110mmHg)
- Traumatic prolonged (> 10 minutes) CPR
- Major surgery less than 3 weeks previously
- History of prior ischemic stroke not within the last 3 months

Cont.

- Dementia
- Recent (2 – 4 wks) internal bleeding
- Non – compressible vascular puncture
- Pregnancy
- Active peptic ulcer
- Current use of an anticoagulant

Summary

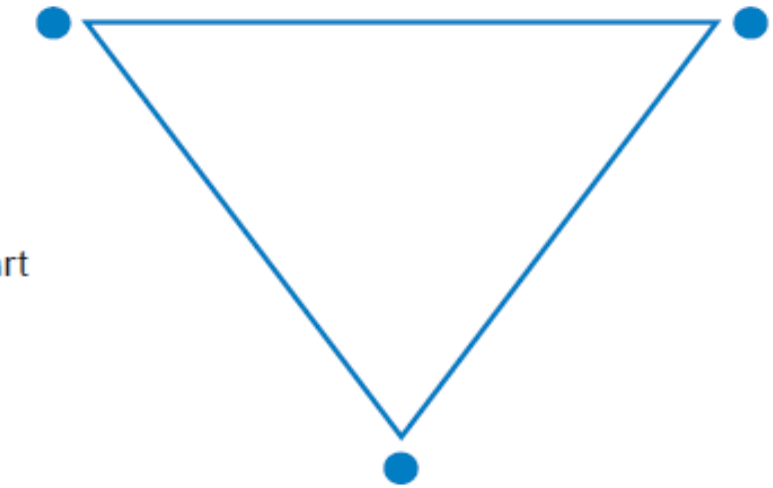
- Thrombolytic therapy if used well is a life – saving medication.

6. TREATMENT OF VENOUS THROMBOEMBOLISM
18/1/2019

BY: DR. M. EZZI

Abnormalities of Blood Flow

- Atrial fibrillation
- Bed rest/immobilization/paralysis
- Left ventricular dysfunction from:
  - ischemic or idiopathic cardiomyopathy, congestive heart failure, or myocardial infarction
- Venous obstruction from tumor, obesity, or pregnancy



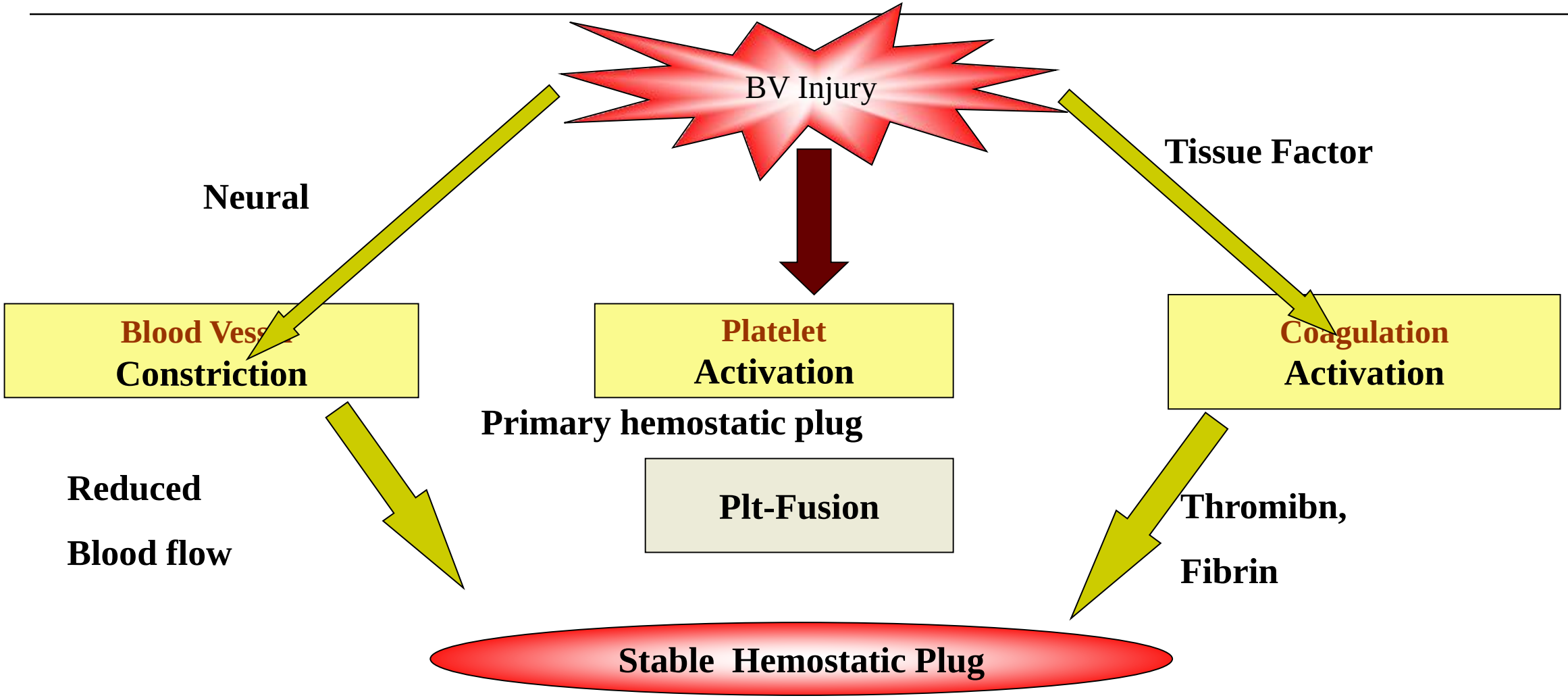
Abnormalities of Surfaces in Contact With Blood

- Acute myocardial infarction
- Atherosclerosis
- Chemical irritation (potassium, hypertonic solutions, chemotherapy)
- Fractures
- Heart valve disease
- Heart valve replacement
- Indwelling catheters
- Previous DVT or PE
- Tumor invasion
- Vascular injury or trauma

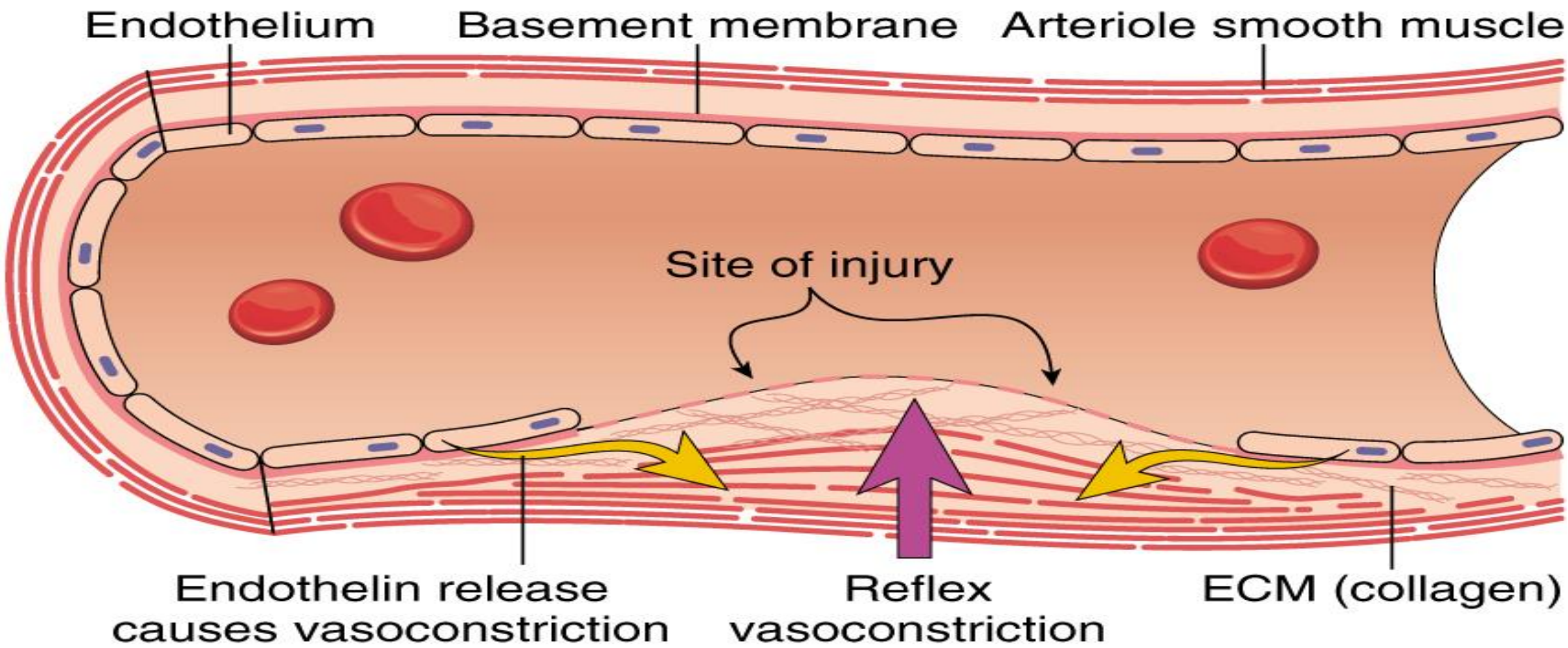
Abnormalities of Clotting Components

- Antiphospholipid antibody syndrome (lupus anticoagulant; anticardiolipin antibody)
- Antithrombin deficiency
- Dysfibrinogenemia
- Estrogen therapy
- Factor V Leiden
- Homocysteinemia
- Malignancy
- Myeloproliferative disorder
- Polycythemia
- Pregnancy
- Protein C deficiency
- Protein S deficiency
- Prothrombin G20210A mutation
- Thrombocytosis

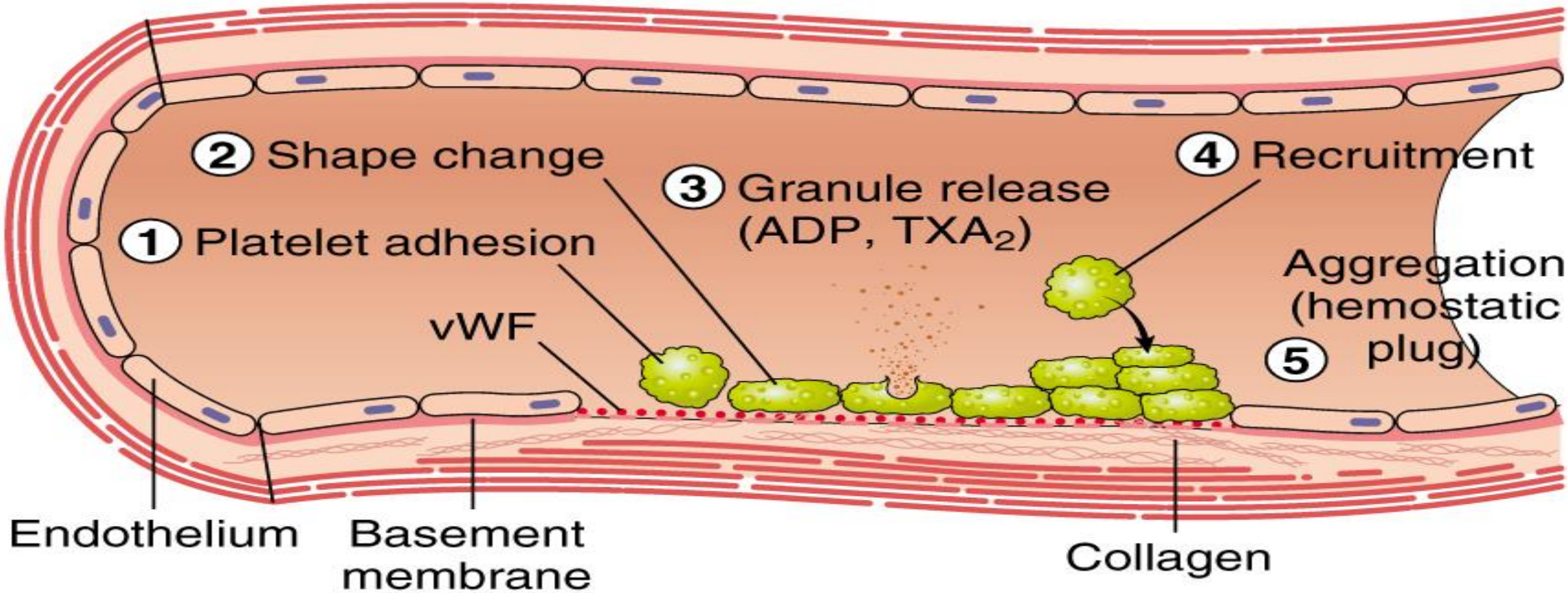
Hemostasis


BV Injury
Neural
Tissue Factor
Blood Vessel
Constriction
Platelet
Activation
Coagulation
Activation
Primary hemostatic plug
Reduced
Blood flow
Plt-Fusion
Thromibn,
Fibrin
Stable Hemostatic Plug

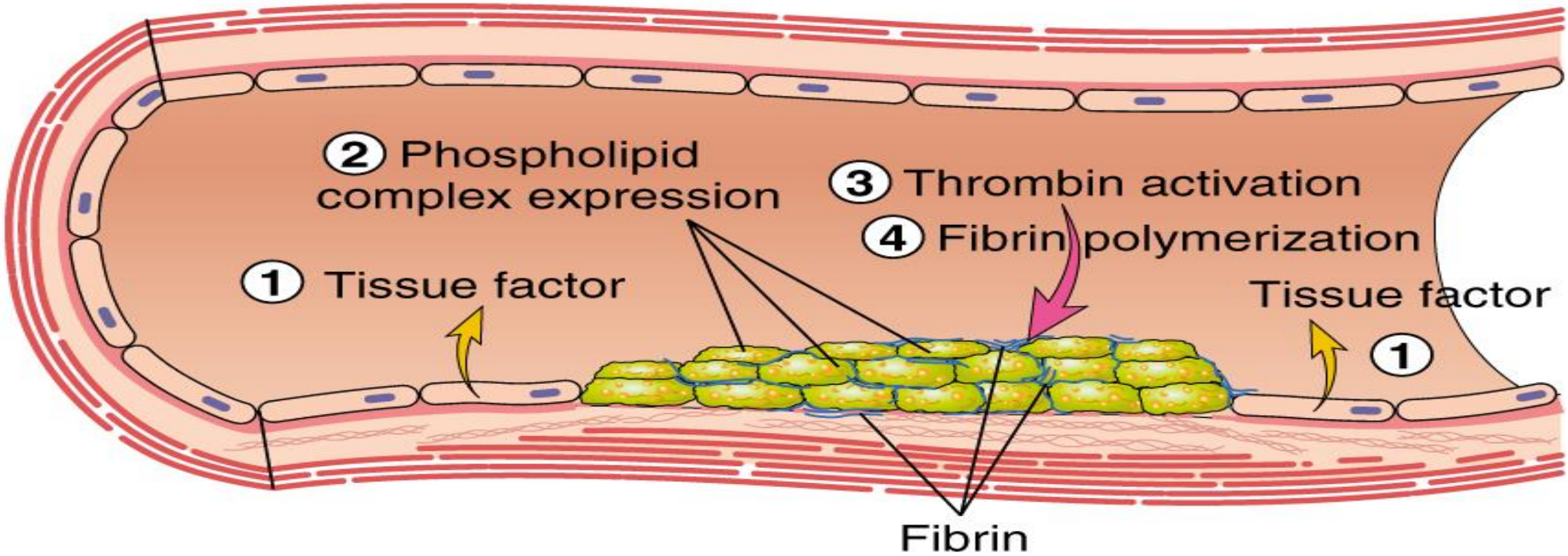
A. VASOCONSTRICTION



B. PRIMARY HEMOSTASIS

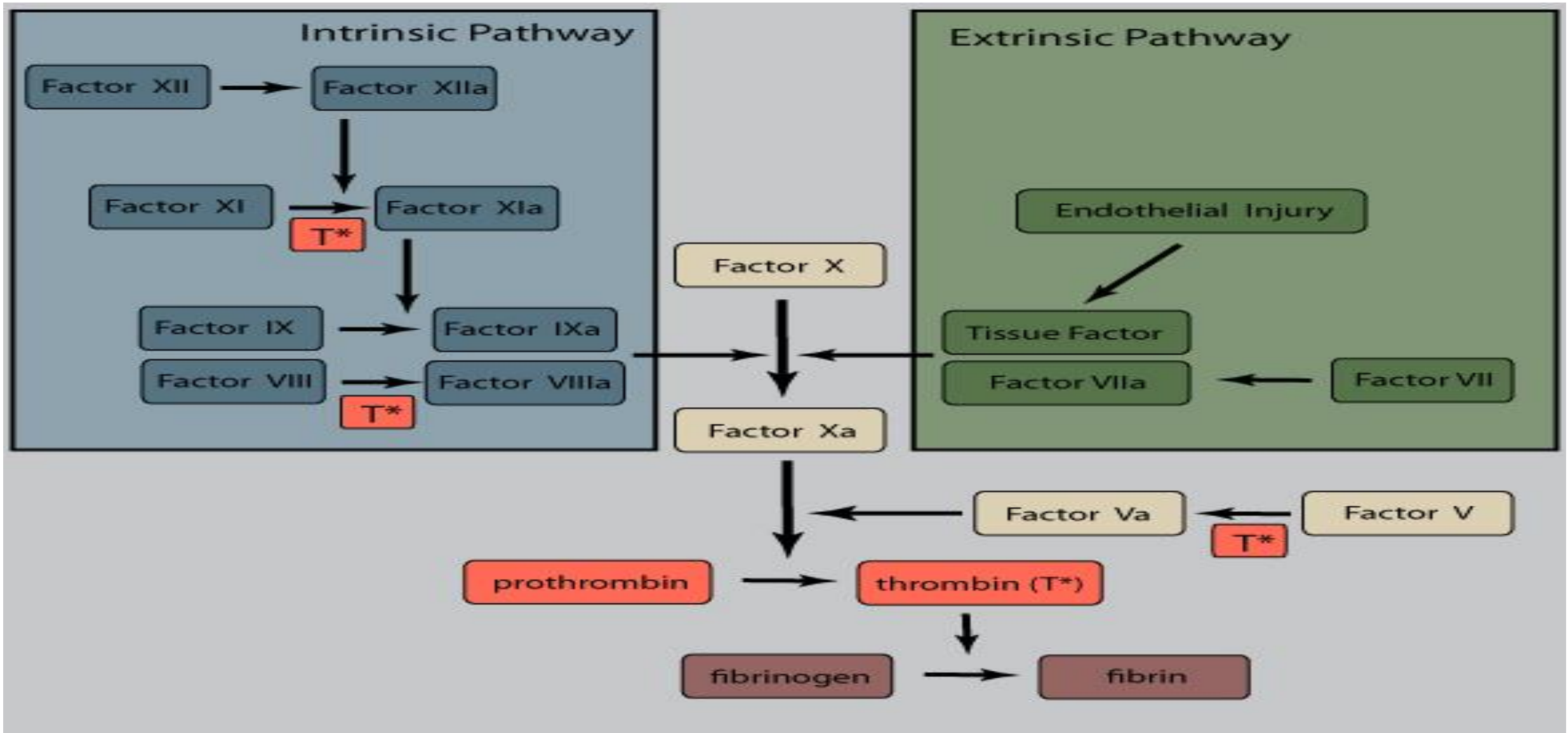


C. SECONDARY HEMOSTASIS



Cont.

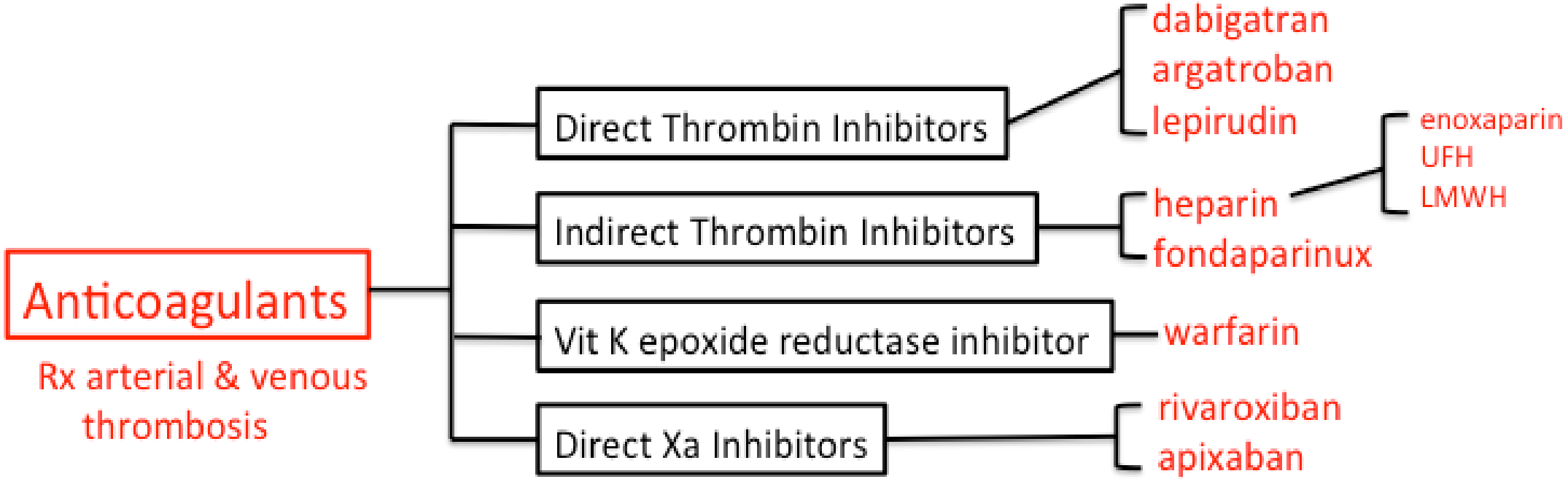
- Drugs used to manage VTE are ***anticoagulants***.
- The coagulation cascade has 2 pathways:
  1. Intrinsic pathway
  2. Extrinsic pathway


Intrinsic Pathway
Factor XII
Factor XIIa
Factor XI
Factor XIa
T*
Factor IX
Factor IXa
Factor VIII
Factor VIIIa
T*
Extrinsic Pathway
Endothelial Injury
Tissue Factor
Factor VIIa
Factor VII
Factor X
Factor Xa
Factor Va
Factor V
T*
prothrombin
thrombin (T*)
fibrinogen
fibrin

Classification of anticoagulants for treatment of arterial and venous thrombosis

1. ***Direct thrombin inhibitors***: dabigatran (only oral drug), argatroban, lepirudin
2. ***Indirect thrombin inhibitors***:
   - Heparin: Enoxaparin, UFH, LMWH
   - Fondaparinux
3. ***Vit K epoxide reductase inhibitors***: Coumarin analogues → warfarin
4. ***Direct X_a inhibitors (novel anticoagulants)***: rivaroxaban, apixaban
   - Don't require frequent plasma level monitoring
   - Given PO

Cont.


Anticoagulants
Rx arterial & venous thrombosis
Direct Thrombin Inhibitors
dabigatran
argatroban
lepirudin
Indirect Thrombin Inhibitors
heparin
enoxaparin
UFH
LMWH
fondaparinux
Vit K epoxide reductase inhibitor
warfarin
Direct Xa Inhibitors
rivaroxiban
apixaban

Ideal anticoagulant

- High efficacy to safety index i.e. wide therapeutic index
- Predictable response (no need for lab)
- Both parenteral and oral
- Rapid onset of action
- Safe antidote
- No side effects
- Minimal drug interaction

Initiation of therapy

- Prompt and optimal anticoagulant therapy
- Treatment options:
  - IV UFH loading followed by infusion
  - SC UFH
  - SC LMWH
  - SC Fondaparinux

Dosing heparin

- 80 units/ kg LD followed by 18 units/kg/hr infusion
  - Faster therapeutic levels
  - Relative resistance to anticoagulation during active clotting

Dose adjustment

- Obtain aPTT 6 hrs. after bolus dose or infusion rate
- Dose adjust accordingly:
  - High (>2.5): reduce dose
  - Low (<1.5): increase dose

TABLE 16-8

Heparin Dosing Nomogram[a]

1. Suggested loading dose
   - Treatment of DVT/PE: 80 units/kg (rounded to nearest 500 units)
   - Prevention, including cardiovascular indications: 70 units/kg (rounded to nearest 500 units)
2. Suggested initial infusion
   - Treatment of DVT/PE: 18 units/kg/h (rounded to nearest 100 units)
   - Prevention, including cardiovascular indications: 15 units/kg/h (rounded to nearest 100 units)
3. First aPTT check: 6 hours after initiating therapy
4. Dosing adjustments: per this chart (rounded to nearest 100 units)

aPTT[b] (seconds)	Heparin Bolus	Infusion Hold Time	Infusion Rate Adjustment	Next aPTT
<50	4,000 units	0	Increase by 200 units/h	In 6 hours
50–59	2,000 units	0	Increase by 100 units/h	In 6 hours
60–100	0	0	None	Every AM
101–110	0	0	Decrease by 100 units/h	In 6 hours
111–120	0	0	Decrease by 200 units/h	In 6 hours
121–150	0	30 minutes	Decrease by 200 units/h	In 6 hours
151–199	0	60 minutes	Decrease by 200 units/h	In 6 hours
>200	0	PRN	Hold until aPTT <100	Every hour until <100

Heparin therapeutic monitoring

- Routine aPTT
  - 6hrs. After any changes
  - Once daily if stable dose
- Evaluate for adverse reactions and treatment failure
- Hb, Hct & PLT count every alternate day

Duration of therapy

- Prolonged anticoagulation
  - Prevents recurrent thrombosis
  - Warfarin preferred (oral started on day 1)
- Heparin for a minimum of 5 days & INR ≥2 for 24 h
- A minimum of 5 days for:
  - Elimination of II & X
  - Full antithrombotic potential

Adverse effects: Thrombocytopenia

- Heparin associated thrombocytopenia (Type I)
  - Direct effect of heparin on platelets
  - Leads to transient platelet sequestration
  - Reversible
  - Occurs in the first 3 days of heparin therapy

Heparin Induced (type II) Thrombocytopenia

- Immune mediated
- Heparin – antibody complex binds to platelets causing aggregation
- Occurs mostly with IV as compared to SC administration
- Paradoxically causes venous and arterial thrombosis
- Intervention: Stop heparin, LMWH now & never rechallenge the patient with heparin again.
- Treatment: DTI – argatroban, lepirudin
- Occurs after day 3 of heparin therapy

Hemorrhage

- Most common adverse effect
- Risk factors:
  - Length of therapy
  - Advanced age
  - Comorbidities
  - Concomitant antithrombotic therapy

Cont.

- Osteoporosis: chronic treatment (6 months)
- Hyperkalemia
  - Inhibition of aldosterone synthesis
  - Risk factors are DM & CKD
- Hypersensitivity reaction
  - Generalized hypersensitivity reactions
  - Priapism
  - Alopecia

Reversal of effects of heparin toxicity

- Discontinue heparin
- Maintain fluid volume
- Replace clotting factors: blood, FFP, concentrates
- Protamine sulfate
  - Forms inactive protamine – heparin complex
  - Rapid onset
  - 1mg for 100IU of heparin (max 50mg)
  - A/E: hypotension, anaphylaxis

Outpatient treatment of DVT

- Uncomplicated DVT
- Patient leaves such that they can get to hospital easily and on time
- Drugs used: LMWH. Fondaparinux
- Administered SC
- Routine monitoring is not required
- Dose adjustment is done in renal failure

Warfarin: transition from injectables

- Start on day 1 with heparin and continue for a minimum of 3 months
- Why overlap? Warfarin has a(n):
  - Half life of > 36 hrs.
  - Elimination rate of clotting factors
  - Initial procoagulant effect of inhibiting protein C & S
  - Adequate anticoagulation

Warfarin initiation

- Complex – varying doses among individuals
- 2 methods:
  - Average daily dosing (4 to 5mg/d) – monitor and adjust
  - 10mg initiation dose for 2 days then adjust accordingly based on the INR

Pharmacogenomic considerations

- 2 major enzymes are associated with warfarin:
  - CYP2C9 which metabolizes warfarin: a mutation in this enzyme warrants a reduction of the warfarin dose due to reduced clearance.
  - Vitamin K Epoxide Reductase 1 (VKORC1): a mutation in this enzyme warrants an increase in the warfarin dose. This is the enzyme inhibited by warfarin.

Warfarin intensity and duration

- INR of 2 to 3 is recommended
  - Maximal antithrombotic effect
  - Minimal bleeding complication
- Initial anticoagulation prevents clot extension. It does not dissolve the clot.
- Continued anticoagulation prevents further clotting

Warfarin intensity & duration

First Event	
Provoked	3 months
Unprovoked	At least 3 months; reevaluate risk–benefit at 3 months indefinite therapy
Unprovoked with proximal presentation and low risk of bleeding	
Cancer-associated	LMWH for 3–6 months, then indefinite therapy or until cancer is resolved
Recurrent Events	
Provoked	Indefinite therapy
Unprovoked	Indefinite therapy

Adverse effects of warfarin - hemorrhage

- Most common
- Risk factors
  - 1st 3 months of therapy
  - History of GI bleeding
  - Comorbidities
  - Concomitant use of antiplatelet and NSAIDs

Skin necrosis

- Rare but serious (5 days therapy)
- Necrosis of breast, buttock & penis
- Extensive microvascular thrombosis (procoagulant)
- Discontinue warfarin (then low dose warfarin)
- Supplement with protein C (FFPs)
- Adequate heparinization (prevention)

Purple toe syndrome

- 6 weeks to therapy
- Painful discoloration of toes due to cholesterol microembolization
- Discontinue warfarin (associated with death)
- DDX: cardiac embolus

Warfarin
factors that influence dosing

- Dietary vitamin K intake
  - High concentrations:
    - Green leafy vegetables
    - Soy milk
    - Vitamin supplements
    - Green tea
    - Tobacco

Cont.

- Comorbidities
  - Diarrhea (reduces vit. K absorption as it is produced by colonic bacteria)
  - Fever (catabolism of clotting factors)
  - Heart failure, liver disease, ESRD (reduced metabolism)
  - Hypothyroidism (reduced catabolism of factors)
  - Hyperthyroidism (increased catabolism of factors)

Cont.

- Alcohol ingestion
  - Chronic alcoholism: induces metabolizing enzymes
  - Acute alcoholic ingestion inhibits metabolic enzymes
- Genetic factors
  - CYP2C9
  - VKORC1
- Concurrent medications

Target	Effect	Response	Examples (not inclusive)			
Clotting factors	Increased synthesis	Decreased INR	Vitamin K			
	Decreased synthesis	Increased INR	Broad-spectrum antibiotics			
	Increased catabolism	Increased INR	Thyroid hormones			
	Decreased catabolism	Decreased INR	Methimazole		Propylthiouracil	
Warfarin metabolism	Inhibition	Increased INR	Acetaminophen Cimetidine Propafenone	Allopurinol Fluroquinolones SSRIs	Amiodarone Macrolides Statins	Azole antifungals Metronidazole Sulfa antibiotics
	induction	Decreased INR	Barbiturates Nafcillin	Carbamazepine Phenytoine	Doxycycline Primidone	Griseofulvin Rifampin
Hemostasis	Additive antithrombotic effects	Increased bleeding risk	Aspirin	NSAIDs	Salicylates	GPIIb/IIIa inhibitors
	Additive anticoagulant response	Increased bleeding risk	Heparin	LMWH	Direct thrombin inhibitors	Thrombolytics
		Decreased INR	Cholestyramine	Colestipol	Sucralfate	
Absorption	Reduced	Decreased INR	Ascorbic acid	Azathioprine	Corticosteroids	Cyclosporine
Unknown		Increased INR	Androgens	Fenofibrate	Cyclophosphamide	Gemfibrozil

Over anticoagulation

- Asymptomatic high INR: withhold therapy
- Minor bleed:
  - Withhold therapy
  - Low dose vit. K
  - Start at a lower dose
- Major bleed:
  - FFPs
  - Factor concentrates
  - High dose vit. K

Prevention

- Low dose UFH
  - Inactivates factor X_a, no effect on FII_a
  - aPTT is not prolonged
- Alternatives
  - Fixed dose SC LMWH
  - SC Fondaparinux

7. PROCOAGULANTS & MANAGEMENT OF BLEEDING 20th/6/2019

BY: DR. KUBO

Phases of hemostasis

- Initiation & formation of the platelet plug
- Propagation of the clotting process by the coagulation cascade
- Termination of clotting by antithrombotic control mechanisms
- Removal of the clot fibrinolysis using the plasminogen activator pathway.

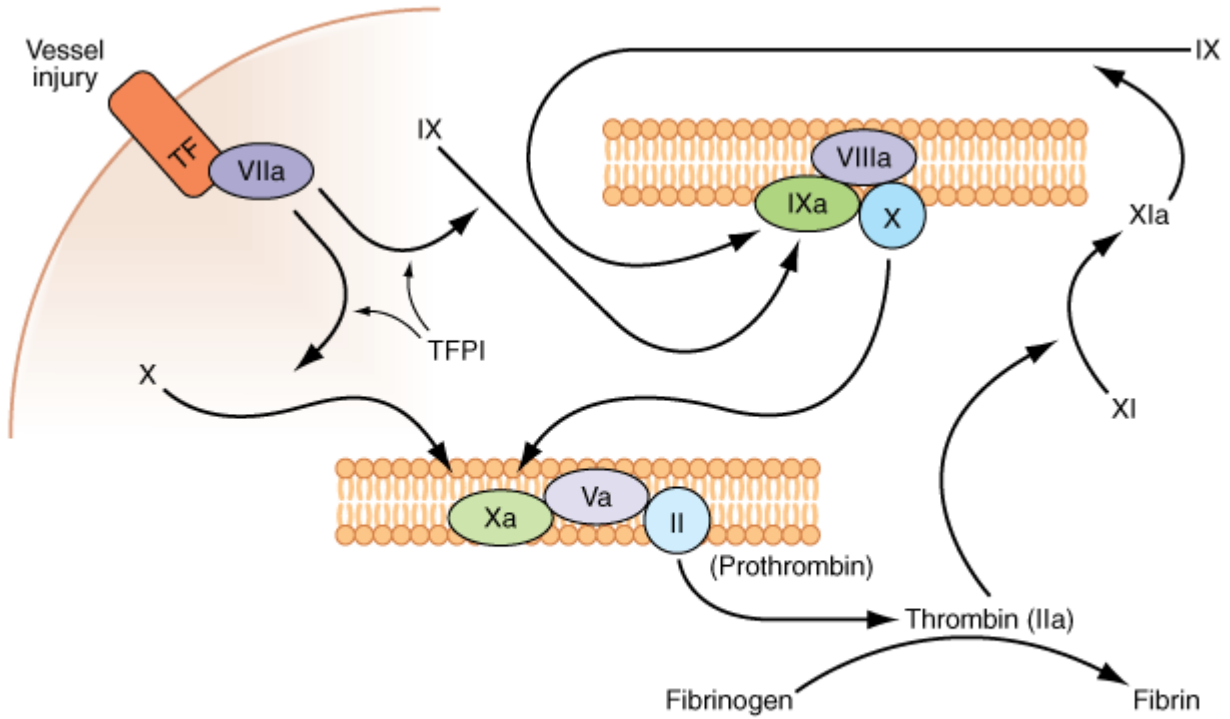
Platelet plug

- ***Adhesion***: to sub endothelial matrix via vWF
- ***Aggregation***: platelet to platelet cohesion via GpIIb/IIIa receptor
- ***Secretion***: release of platelet granule proteins (ADP, thromboxane A_2)
- ***Procoagulant activity***: enhancement of thrombin generation

Coagulation cascade**

- Intrinsic pathway (tested via aPTT)
- Extrinsic pathway (most important)
  - Starts with FVII (tested via PT)
- Common pathway
  - FX → FV → FII
  - Stabilizations of fibrin: FIII

Cont.



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

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Causes of bleeding

Platelet plug disorders

- Adhesion: von Willebrand Disease, Bernard Soulier (Lack of glycoprotein I receptors)
- Aggregation: Glanzmann's thrombasthenia, afibrinogenemia
- Secretion:
  - Cox inhibition by NSAIDs: thromboxane is not synthesized
  - Uremia
- Procoagulant activity: Scott's syndrome

Cont.

Systemic diseases that cause or exacerbate bleeding:

- Liver disease (reduces production of coagulation factors)
- Severe renal failure → Uremia →
  - BM suppression
  - Reduced platelet function
- BM failure

Cont.

- DIC (consumptive coagulopathy)
- Thrombocytopenia: ITP, hypersplenism, Heparin Induced Thrombocytopenia,
- Drug history: Warfarin, Heparin
- Coagulation deficiencies: Hemophilia, Christmas disease

Clinical manifestations of disordered hemostasis

Clinical characteristic	Bleeding disorder	
	Platelet defect	Clotting factor deficiency
Site of bleeding	Skin, mucous membranes (gingivae, nares, GI and genitourinary tracts)	Deep in soft tissues (joints, muscles)
Bleeding after minor cuts	Yes	Not usually
Petechiae	Present	Absent
Ecchymoses	Small, superficial	Large, palpable
Hemarthroses, muscle hematomas	Rare	Common
Bleeding after surgery	Immediate, mild	Delayed, severe

Petechiae in ITP

Management of bleeding

- Depends on cause
- Initial management may involve resuscitation
  - Large bore IV (14G or 16G)
  - GXM
  - Pressure application if superficial
  - Crystalloids/ colloids

Procoagulants

1. Vitamin K
2. Plasma fractions
   - Factor concentrates
   - Cryoprecipitate
   - FFP
3. Desmopressin acetate
4. Tranexamic acid
5. Ethamsylate

Vitamin K

- Involved in post – ribosomal modification of factors II, VII, IX & X
- Fat soluble; requires bile salts for absorption
- 2 natural forms
  - Vitamin K_1 (***phytonadione***) in green leafy vegetables
  - Vitamin K_2 (***menaquinone***) synthesized by intestinal bacteria
- The water – soluble salt of vitamin K_3 (***menadione***) is not used in therapeutics as it is associated with ***hemolytic anemia*** & ***neonatal hepatic damage***.

Vitamin K1

- Available in oral and parenteral forms
  - Choice depends on how patient has presented
- Onset of effect is delayed for 6 hrs.
  - Administer FFP whose onset kicks in immediately.
- Rapid IV administration can produce dyspnea, chest pain, back pain & death this infuse slowly.
- Subcutaneous administration results in erratic absorption.

Clinical uses

- Given to all newborns to prevent hemorrhagic disease of the newborn (***0.5 – 1mg*** IM within an hour of birth).
- Treating depression of prothrombin activity by excess warfarin or vitamin K deficiency.

2. Plasma Fractions

Factor	Deficiency State	Source
I	Hypofibrinogenemia	Cryoprecipitate (contains fibrinogen, FVIII, FXIII & vWF)
II	Prothrombin deficiency	Prothrombin complex concentrate
V	Factor V deficiency	FFP
VII	Factor VII deficiency	FFP, Recombinant factor VIIa
VIII	Hemophilia A (Classic hemophilia)	Recombinant Factor VIII products, Cryoprecipitate, DDAVP

Cont.

Factor	Deficiency State	Source
IX	Hemophilia B (Christmas disease)	Recombinant Factor IX products
X	Stuart – Prower factor deficiency	FFP, Prothrombin complex concentrates
XI	Hemophilia C	FFP
XII	Hageman defect	Treatment not necessary
Von Willebrand	Von Willebrand disease	Intermediate purity Factor VIII concentrates that contain von Willebrand factor
XIII	Factor XIII deficiency	FFP, Cryoprecipitate

Factor VIII & IX Concentrates

- Spontaneous bleeding occurs when factor activity is < ***5 – 10% of normal***.
- May be ***plasma derived*** or ***recombinant***.
- Prepared from plasma → heat- or detergent- treated (eliminates HIV/HBV/HCV but not prions).
- Intermediate purity factor VIII concentrates e.g. ***Humate P*** contain significant amounts of vWF.
- vWF binds FVIII and the half life of FVIII when bound to vWF is 12 hrs. If vWF is reduced, the half life is reduced to 1 – 2 hrs.
- Half life of FIX is 24 hrs. hence can be administered once daily.

Dosing

Factor VIII

- Each unit/kg raises its activity in plasma by 2%.
- Initial loading dose is ***50 units/kg*** to achieve 100% activity (if baseline was <1%).
- Given BD.

Factor IX

- Therapy requires twice the dose of Factor VIII.
- Given OD (longer $t_{1/2}$).

Clinical uses

Clinical situation	Therapeutic goal (% of normal factor level)
Uncomplicated hemorrhage into a joint	Maintain factor level at least 30-50% of normal concentration for at least 24hrs
Soft tissue hematomas	100% activity for 7 days
Hematuria	10% activity for 3 days
Surgery & major trauma	100% activity for 10 days

Cryoprecipitate

- Contains
  - Fibrinogen (300mg/unit)
  - Factor VIII
  - Factor XIII
  - vWF
- The concentration of FVIII & vWF is less than that found in the individual concentrated plasma fractions.

Clinical uses

- Fibrinogen deficiency/ qualitative defects e.g.. DIC, liver disease.
- Factor VIII or vWF deficiency: if pathogen inactivated product unavailable.
  - Cryoprecipitate is not treated in any manner to ↓ risk of viral exposure.
- Rh negative women should receive only Rh – negative cryoprecipitate because of possible contamination of the product with Rh – positive blood cells.
  - May result in hydrops fetalis in a subsequent pregnancies in Rh –ve women.

Fresh Frozen Plasma

- Prepared from whole blood & frozen at ***-18 to -30°C***.
- Contains all the coagulation factors.
- Used to correct bleeding due to deficiency of ***multiple factors*** e.g. in:
  - Warfarin overdose
  - Vitamin K deficiency
  - Liver failure
  - Dilutional coagulopathy following massive transfusion
- Dose: ***10 – 15ml/kg.***

Other Factor Concentrates

- ***Autoplex*** & ***FEIBA*** **(F**actor **E**ight **I**nhibitor **B**ypassing **A**ctivity**)** contain *activated* clotting factors.
  - Useful in patients with inhibitors or antibodies to factor VIII or factor IX.
- ***NovoSeven***: Recombinant activated factor VII
  - Used to treat coagulopathy associated with liver disease and major blood loss in trauma and surgery.

Desmopressin Acetate (DDAVP)

- ↑s factor VIII activity in patients with:
  - Mild hemophilia A
  - vWD
- It ***promotes the release of vWF & FVIII from endothelial cells***
- It can be used in preparation for minor procedures e.g. tooth extraction (parenteral prophylactic desmopressin)
- High dose intranasal desmopressin may be used.

ε - Aminocaproic Acid (EACA)

- Synthetic inhibitor of fibrinolysis.
- Competitively inhibits plasminogen activation.
- Rapid oral absorption
- Renal excretion
- **Tranexamic acid** is an analog of aminocaproic acid.
  - Dose: 30mg/kg QID

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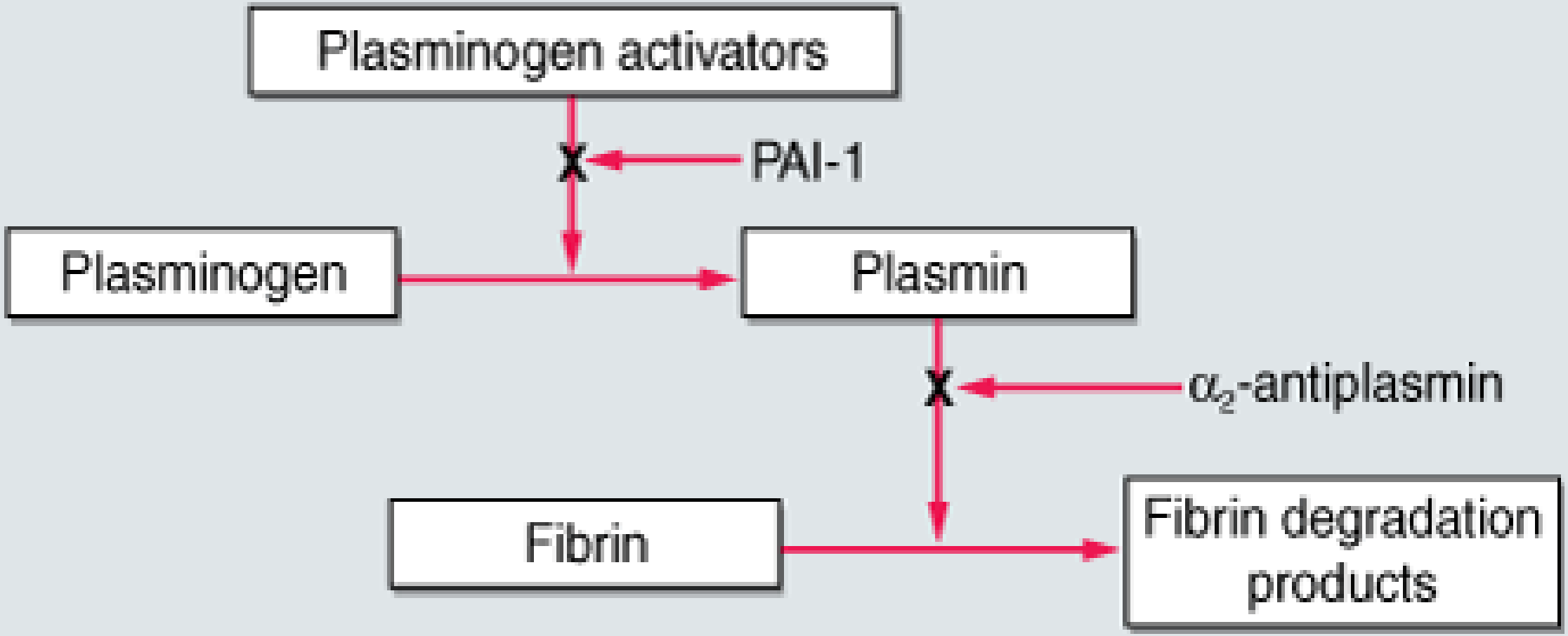

Plasminogen activators
X
PAI-1
Plasminogen
Plasmin
X
α_2-antiplasmin
Fibrin
Fibrin degradation products

Clinical uses

1. Adjunctive therapy in hemophilia
2. Bleeding from excessive fibrinolytic therapy
3. Prophylaxis for rebleeding from intracranial aneurysms
4. Postsurgical bleeding: GI, prostatectomy
5. Bladder hemorrhage 2^{0} radiation or drug – induced cystitis (cyclophosphamide)

Adverse effects

- Intravascular thrombosis, hypotension, myopathy, diarrhea, & nasal stuffiness.
- ***Contraindicated*** in DIC or upper urinary tract bleeding (renal/ureteric) → potential for excessive clotting.

Ethamsylate

- Synthetic hemostatic drug
- Mechanism of action:
  - Improves platelet adhesiveness
  - ↑s capillary endothelial resistance
  - Inhibits biosynthesis of prostacyclin which causes platelet disaggregation & vasodilation.

Cont.

Indications

- Menorrhagia
- Metrorrhagia
- Post abortion & postpartum hemorrhage

Adverse effects

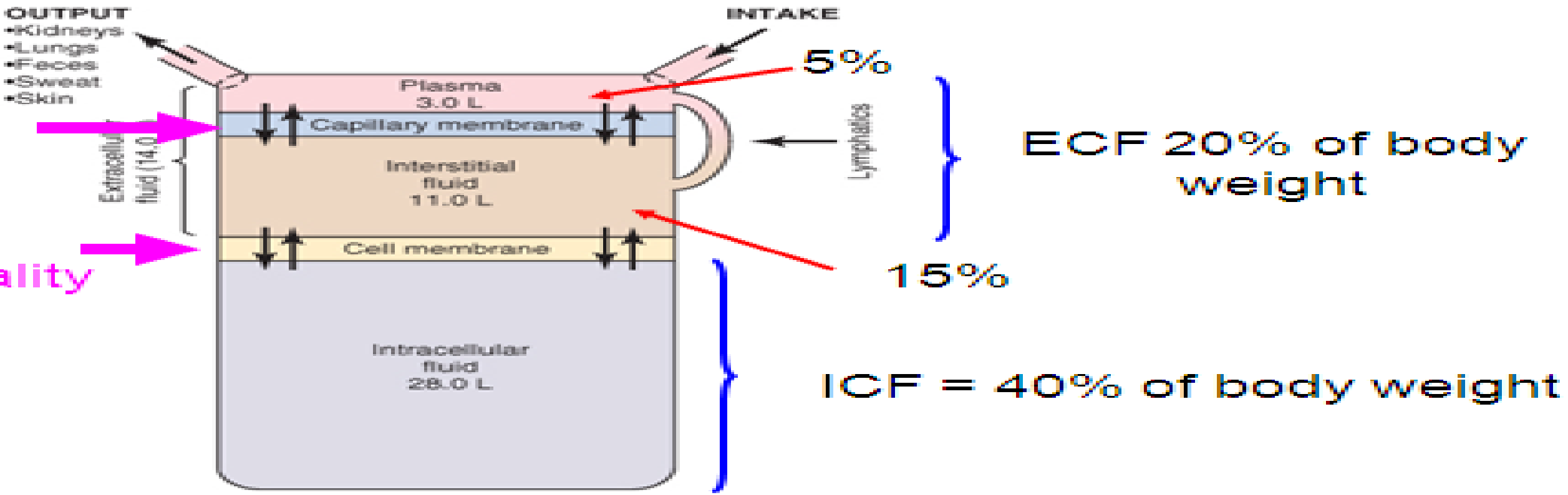
- Hypotension
- Headache
- Rash
- Nausea.

8. INTRAVENOUS FLUIDS 9/5/2019

BY: DR. KUBO

Fluid compartments

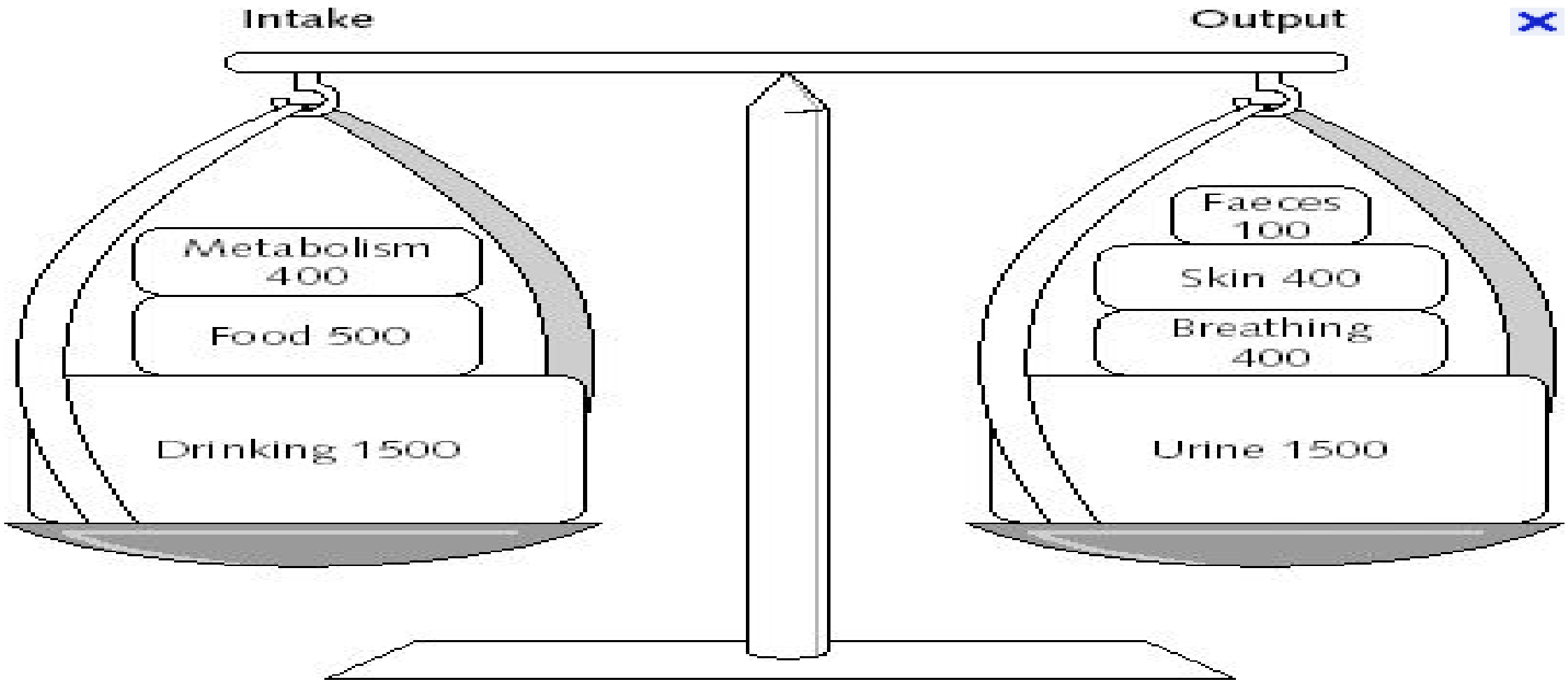
60-70% of total body weight is made up of water



Delicate balance

- Fluid input = output
  - ***To monitor input & output of fluid, ensure urinary catheterization if the patient is not voiding urine normally***.
- On average, an adult input & output is 30 – 35 ml/kg/d (about 2.4L/d)

Cont.


Intake
Output
Metabolism 400
Food 500
Drinking 1500
Faeces 100
Skin 400
Breathing 400
Urine 1500

Components of fluid therapy

- ***Maintenance therapy***: replaces ongoing losses of water & electrolytes under normal physiologic conditions via urine, sweat, respiration and stool.
  - ***Usually 2 – 3L per 24h***
- ***Replacement therapy***: corrects any existing water & electrolyte deficits e.g. in severe vomiting & diarrhea, DKA

Increased fluid requirements are seen in

- Fever: every ^{0}C increase of body temp. above 37^{0}C increases fluid requirements by 100 – 150mL/d)
- Burns (>30% BSA)
- Skin failure syndromes e.g. TEN
- Surgical drains
- GIT losses: vomiting, diarrhea
- Sweating
- Tachypnea
- Polyuria: DM, DI

Definition

- ***Osmolality***: refers to solute concentration in the body fluid **by weight** (I.e., the number of milliosmoles in a kg of solution)
  - Humans: normal osmolality = **275 – 295 mOSm/Kg**
- ***Osmolarity***: number of solute particles **per liter of solvent**.

Which fluid, when?

- Normal saline
- Ringer's lactate
- 5% dextrose
- Half Normal Saline (HNS)
- Albumin

Types of IVFs

1. Crystalloids
2. Colloids
3. Blood & its products

1. Crystalloids

- Contain ***small molecules that flow easily across cell membranes*** → allows for transfer from blood to cells & body tissues.
- They increase fluid volume in both the interstitial & intravascular spaces (extracellular)
- Divided into:
  1. Isotonic
  2. Hypotonic
  3. Hypertonic

a. Isotonic Fluids

- Include:
  i. Normal saline (0.9% sodium chloride)
  ii. Ringer's lactate (LR)
  iii. 5% dextrose (D5W)
  iv. Ringer's solution
- Indication: intravascular volume expanders e.g. in hypovolemic shock.

Cont.

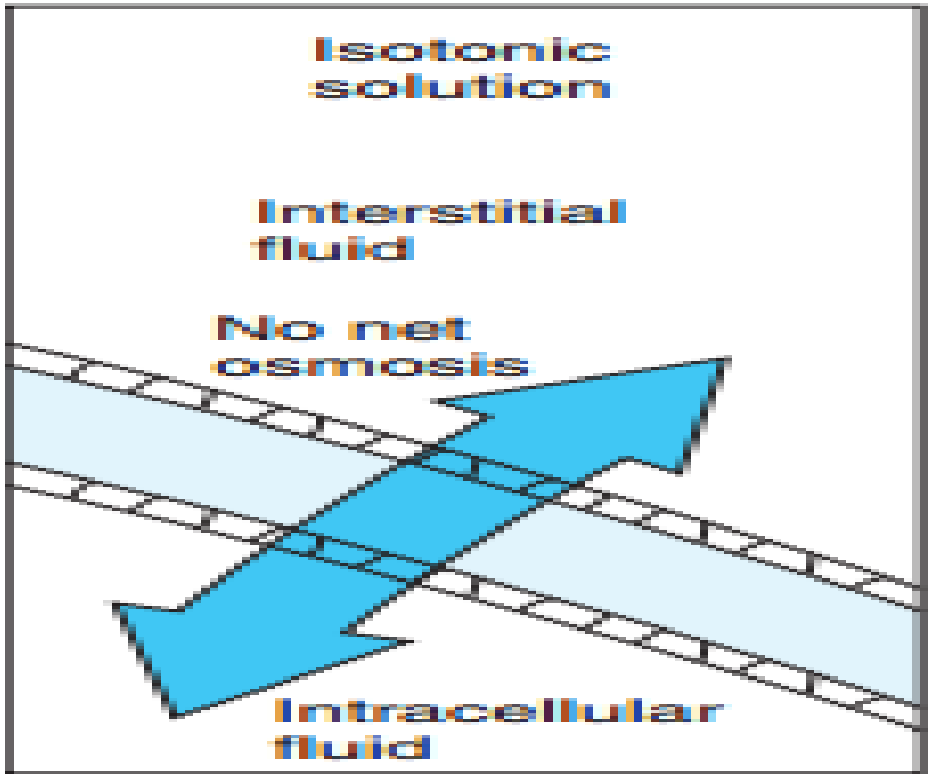


Figure 3–2. Isotonic solutions do not result in any significant fluid shifts across cellular or vascular membranes.

i. Normal Saline (0.9% NaCl)

Solutions	Na^+ (mEq/L)	K^+ (mEq/L)	Ca^{2+} (mEq/L)	Mg^{2+} (mEq/L)	Cl^- (mEq/L)	HCO_3^- (mEq/L)	Dextrose	mOsm/L
0.9% NaCl	154				154			308

Indications

- Correction of fluid volume deficit from: hemorrhage, severe vomiting or diarrhea, heavy drainage from GI suction, fistulas, wounds
- Shock
- Mild hyponatremia
- Metabolic acidosis e.g. DKA
- ***Fluid of choice for resuscitation efforts as whole blood is being sought.***

ii. Ringer's Lactate (Hartmann's solution)

Solutions	Na^+ (mEq/L)	K^+ (mEq/L)	Ca^{2+} (mEq/L)	Mg^{2+} (mEq/L)	Cl^- (mEq/L)	HCO_3^- (mEq/L)	Dextrose	mOsm/L
Lactated Ringer's	130	4	3		109	28		273

Indications:

- Replace GIT fluid losses: diarrhea or vomiting
- Fistula drainage
- Fluid losses due to burns & trauma
- Patients experiencing acute blood loss or hypovolemia
- NB: both 0.9% NaCl & LR may be used in many situations, but ***patients requiring electrolyte replacement e.g. surgical or burn patients will benefit more from an infusion of LR.***

Cont.

- LR is metabolized in the liver where lactate is converted to bicarbonate. In lieu of this, caution should be taken in patients with:
  - Liver disease: failure/ defective metabolism of lactate may result in accumulation & lactic acidosis.
  - Severe renal impairment: hyperkalemia may result due to impaired excretion of extra K^+
  - Alkalosis (pH > 7.5): as accumulation of bicarbonate from lactate breakdown will exacerbate the alkalosis.

iii. 5% Dextrose in Water (D5W)

Solutions	Na^+ (mEq/L)	K^+ (mEq/L)	Ca^{2+} (mEq/L)	Mg^{2+} (mEq/L)	Cl^- (mEq/L)	HCO_3^- (mEq/L)	Dextrose	mOsm/L
D5W							50g/L	278

- Considered an isotonic solution but ***when the dextrose is metabolized the solution actually becomes hypotonic & causes fluid shift into cells (beneficial in cellular dehydration e.g. in hypernatremia)***
- Provides free water that passes through membrane pores to both IC & EC spaces, expanding both compartments simultaneously.
- Provides ***170 calories/ liter*** → can provide nutrition while the patient is NPO, but this is not enough for prolonged periods.

Precautions with D5W

- Avoid in renal or cardiac failure → ***can cause or worsen fluid overload***
- May ***increase risk of cerebral edema*** in patients with increased ICP as the hypotonic solution will be drawn into the brain cells.
- Shouldn't be used in isolation to treat fluid volume deficit → ***dilutes plasma electrolyte concentrations***.
- Not used for resuscitation as the solution won't remain in the intravascular space; ***once glucose is metabolized it becomes hypotonic and the water is drawn out of the intravascular space***.

iv. Ringer's solution

Solutions	Na^+ (mEq/L)	K^+ (mEq/L)	Ca^{2+} (mEq/L)	Mg^{2+} (mEq/L)	Cl^- (mEq/L)	HCO_3^- (mEq/L)	Dextrose	mOsm/L
Ringer's solution	130	4	3		109	28		273

- Similar in composition as LR except does not have lactate hence the contraindications related to lactate do not apply for ringer's solution.

b. Hypotonic fluids

- Have a lower concentration of solutes (***osmolarity < 250 mOsm/L***)
- Lower the serum osmolarity within the vascular space.
- Cause fluid to shift from the intravascular space to both the intracellular & interstitial spaces.
- These solutions will hydrate cells e.g. in hypernatremia

Cont.

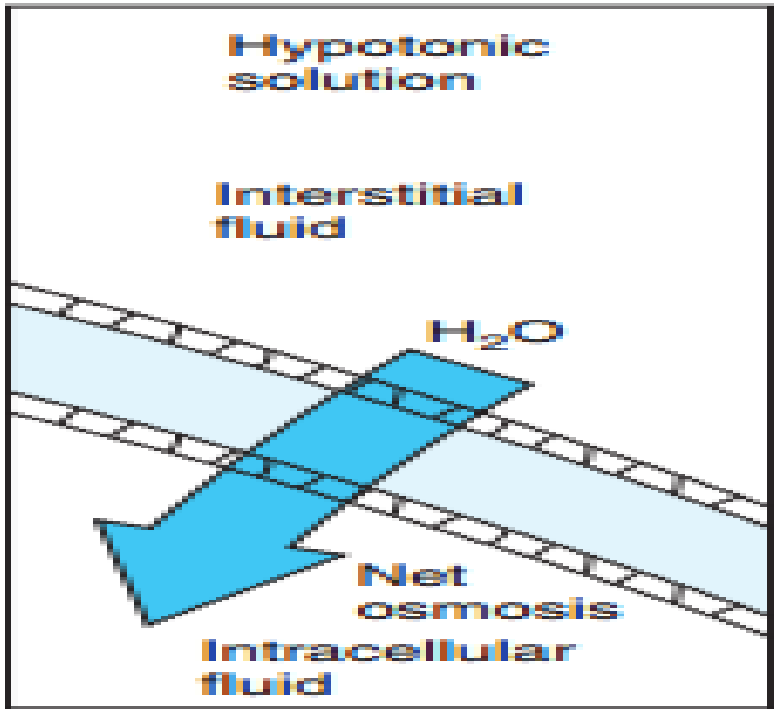


Figure 3–4. A hypotonic solution given IV will cause fluids to leave the vasculature for the interstitial and intracellular spaces.

Include:

- 0.45% NaCl
- 0.33% NaCl
- 0.2% NaCl
- 2.5% dextrose in water

Indications

- Situations associated with intracellular dehydration, when fluid needs to be shifted into the cell e.g. hypernatremia.

Precautions

- May exacerbate cerebral edema.
- May deplete intravascular volume in patients with burns, trauma → ***worsen existing hypovolemia and hypotension and cause cardiovascular collapse***.

c. Hypertonic fluids

- Have a high solute concentration (osmolality ≥ 375 mOsm/L)
- The osmotic pressure gradient draws water out of the intracellular space, increasing the ECF volume, so they are used as ***volume expanders***.

Cont.

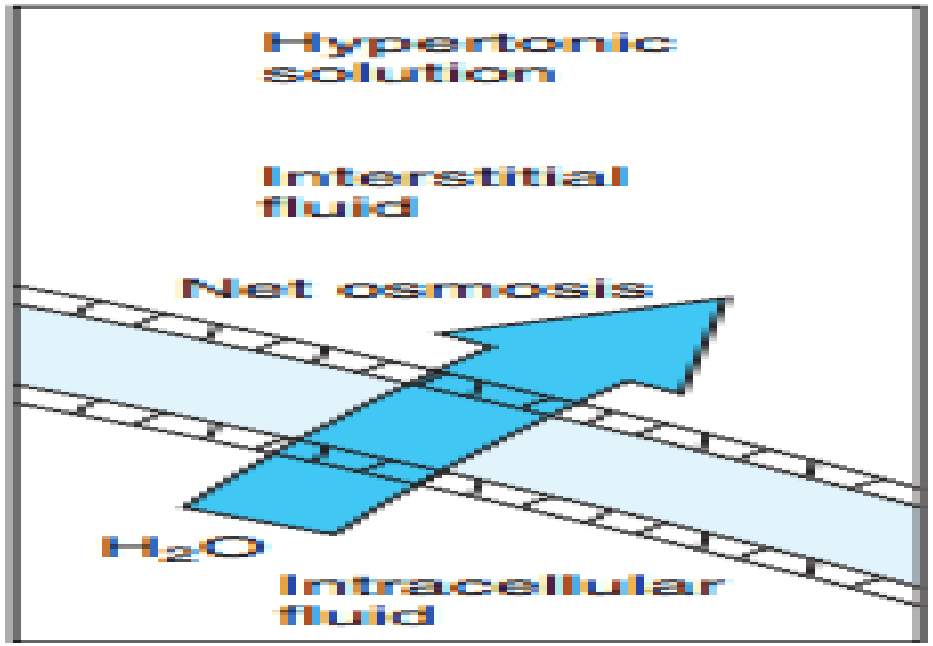


Figure 3-3. A hypertonic solution given IV will draw fluids from the cells and interstitial spaces into the vasculature.

examples

- 3% NaCl
  - Used in cases of ***severe hyponatremia***
  - May be benefit in cerebral edema
- 5% dextrose with NS (D5NS)
  - Replaces sodium, chloride & some calories

Precaution

- Potential to cause intravascular fluid volume overload (***hydrostatic pressure increases***) & pulmonary edema thus constantly monitor the patient's vital signs (look out for elevated BP & RR).

2. Colloids

- HMW substances that largely remain in the intravascular compartment, thereby generating an oncotic pressure.
- Expand the intravascular volume by drawing fluid from the interstitial spaces into the intravascular compartment.
- Similar effect as ***hypertonic crystalloids*** but:
  - Require administration of less total volume
  - Have a longer duration of action as the molecules remain within the intravascular space longer.

Types

- Natural: 5% albumin (Human albumin solution)
- Artificial:
  a. Dextran
  b. Gelatin
  c. Hydroxy – ethyl starches

a. 5% albumin

- MC used colloid
- Contains plasma protein fractions obtained from ***human plasma***
- Rapidly expands plasma volume
- Considered a blood transfusion product → requires all the same nursing precautions used when administering other blood products; monitor for anaphylaxis
- Expensive
- Effects lasts 16 – 24 h
- Indications:
  - Volume expansion in shock states
  - Moderate protein replacement in hypoalbuminemic states

b. Dextran

- 2nd MC used
- Polysaccharide
- Effects lasts 6 – 12h
- Disadvantages
  - Anaphylaxis
  - Coagulation abnormalities: reduces platelet adhesiveness, reduce FVIII levels
  - Interferes with cross matching of blood by coating RBCs (***always take blood for GXM before giving dextran***)
  - May plug renal tubules precipitating ARF

c. Hydroxyethyl starches

- Examples: Hetastarch, Pentastarch, Tetrastarch
- Less expensive than albumin.
- Used for hemodynamic volume replacement following major surgery and to treat burns.

d. Gelatins

- LMW proteins formed from hydrolysis of collagen.
- Duration of action is shorter compared to albumin & starches.
- Examples: Polygeline (Haemacel)

Precautions with use of colloids

- Monitor for signs of fluid overload.
- Can interfere with platelet function & increase bleeding times, so monitor the patient's coagulation indices.
- May cause anaphylactoid reactions (rare).

Typed By Naila Kamadi

The Gospel ABCs

Admit you're a sinner. (Rom. 3:23)

Believe the Lord Jesus. (John 3:16)

Confess the Lord Jesus. (Rom 10:9)

Salvation prayer

~ Life is too short. Tomorrow is never promised.~

~Jesus loves you ☺ ~

3. RESPIRATORY THERAPEUTICS NOTES. LEVEL VI MBCHB 2019

COMPILED BY NAILA KAMADI

OUTLINE

- Management of Pneumonias
- Treatment of Tuberculosis
- Management of COAD
- Treatment of Bronchial Asthma

1. MANAGEMENT OF PNEUMONIAS
29/1/2019

BY: DR. MUASYA

TYPED BY NAILA KAMADI

Definition

- Pneumonia is an infection of the pulmonary parenchyma.

Classification

- Pneumonias are typically classified as being either:
  1. Community Acquired Pneumonia (CAP) or
  2. Health – Care Associated Pneumonia (HCAP) → previously termed nosocomial pneumonia

1. COMMUNITY ACQUIRED PNEUMONIA (CAP)

Essentials of diagnosis:

- Symptoms & signs of acute lung infection:
  - Fever or hypothermia
  - Cough ± sputum
  - Dyspnea
  - Chest discomfort
  - Sweats or rigors
  - Bronchial breath sounds or rales are frequent auscultatory findings
  - Parenchymal infiltrates on CXR

Cont.

- Occurs *outside the hospital* or < *48h after admission* in a patient who is not:
  - Hospitalized or
  - Residing in a long – term care facility for ≥ 14 days before the onset of symptoms.

Pathogenesis of CAP

- Pulmonary defense mechanisms (cough reflex, mucociliary clearance system, immune responses) normally prevent the development of LRTIs following aspiration of oropharyngeal secretions containing bacteria or inhalation of infected aerosols.
- CAP occurs when *there is a defect in one or more of the normal pulmonary host defense mechanisms*, or when a *very large infectious inoculum* or a *highly virulent pathogen* overwhelms the host.

Important risk factors for increased morbidity & mortality from CAP

- The CURB – 65 criteria may be used as a severity of illness score

  Includes 5 variables:

  - **C**onfusion: altered mental status
  - **U**rea > 7 mmol/L
  - **R**R of ≥ 30 breaths/min (adult)
  - **B**P ≤ 90/60 mmHg → Hypotension
  - Age of ≥ **65** years → advanced age

Interpretation of the CURB – 65 score

- Patients with a score of **0** would have a 30 day mortality rate of 1.5% and can be treated as **outpatient**.
- Patients with a score of **2** would have a 30 day mortality rate of 9.2% and should be **admitted**
- Patients with a score of ≥ **3** have a mortality rate of 22% overall → these patients may require admission to **ICU**

Comorbid medical conditions associated with increased morbidity & mortality from CAP

- Neoplastic disease
- Liver disease
- CCF
- Cerebrovascular disease
- Renal disease

Causes of CAP

- **Bacteria** are more commonly identified than viruses.
- The MC bacterial pathogen identified is *S. pneumoniae* accounting for approx. 2/3 of bacterial isolates
- ≥ 2 causes are identified in up to 5% of cases.

Other common bacterial pathogens include:

- *H. influenzae*
- *M. pneumoniae*
- *Chlamydia pneumonia*
- *S. aureus*
- *Neisseria meningitidis*
- *M. catarrhalis*
- *Klebsiella pneunoniae*
- Other gram –ve rods
- *Legionella species*

Common viral causes of CAP

- Influenza virus
- RSV
- Adenovirus
- Parainfluenza virus

Treatment considerations for CAP

- It is difficult to consistently differentiate bacterial from viral causes or typical from atypical (e.g. chlamydia & other viruses) causes of pneumonia.
- As a result, recommendations for empiric treatment should be based on epidemiologic data.
- Can be divided into those for patients who can be treated as outpatient and those who require hospitalization.

Outpatient treatment

- Empiric antibiotic therapy is largely directed to Strep pneumoniae infections. 3 scenarios are presented:
  1. Treatment of mild CAP
  2. Other treatment options in a previously healthy patients who has had no antibiotics in the past 3 months and who doesn’t require admission
  3. Treatment of an outpatient with comorbidities & antibiotic use in the past 3 months

Treatment of mild CAP

- **Oral Amoxicillin** is the preferred antibiotic at a dose of at least **500mg 8hrly.**

Other treatment options for a patient with CAP who was previously healthy & has had no antibiotics in the past 3 months and who doesn't require admission:

- Macrolides
  - Clarithromycin 500mg PO BD
  - Azithromycin 500mg PO OD for 3 days
  - Erythromycin (250 – 500mg PO QID)

Cont.

- Doxycycline 100mg PO BD
- Fluoroquinolones (with enhanced activity against *Strep. Pneumoniae* i.e., respiratory fluoroquinolones)
  - Gatifloxacin 400mg PO OD
  - Levofloxacin 500 – 750 mg PO OD
  - Moxifloxacin 400mg PO OD
    - ***READ ABOUT RECENT ADVISORY ABOUT USE OF FLUOROQUINOLONES.***

Alternative treatment for CAP

- Amoxicillin – potassium clavulanate – esp. for *suspected aspiration pneumonia* at 500mg PO TDS (625 mg) or 875 mg PO BD (1g)

Cont.

- Some 2nd & 3rd generation cephalosporins such as,
  - Cefuroxime axetil (250 – 500mg PO, BD)
  - Cefpodoxime proxetil (100 – 200 mg PO BD)
  - Cefprozil (250 – 500mg PO, BD)

Treatment of an outpatient with comorbidities or with antibiotic use in the past 3 months

- Select an alternative from a different class, either:
  - A respiratory fluoroquinolone (FQ)
  - A beta – lactam plus a macrolide

Cont.

- Preferred beta lactams:
  - High dose amoxicillin 1g TID; amoxicillin/ clavulanate (2g BD)
- Alternatives:
  - Ceftriaxone 1 – 2g IV BD
    Cefpodoxime 200mg PO BD
  - Cefuroxime 500mg PO BD

Recommendations for duration of treatment

- This is influenced by:
  - Severity of illness
  - Etiologic agent
  - Response to therapy
  - Other medical conditions
  - Complications

Cont.

- As a rule, ***treat for a minimum of 5 days***
- Continue treatment until a patient is afebrile for at least 48 – 72 hrs.
  - This is usually sufficient for pneumonia due to *S. pneumoniae*.

Cont.

- A minimum of 2 weeks of treatment is appropriate for pneumonia due to the following:
  - *S. aureus*
  - *P. aeruginosa*
  - *Klebsiella*
  - Anaerobes
  - *Mycoplasma pneumoniae*
  - *Chlamydia pneumoniae*
  - *Legionella spp.*

Treatment of hospitalized patients

- Empiric antibiotic treatment for patients with CAP who require hospitalization can be divided into:
  - Patients who can be treated in a general medical ward.
  - Patients who require treatment in an ICU.

Patients who only require general medical ward care usually responds to:

- An extend spectrum beta lactam (such as **ceftriaxone** or **cefotaxime**) plus a **macrolide** (clarithromycin or azithromycin is preferred if *H. influenzae* infection is suspected)
- A respiratory FQ

Alternative treatment for a general medical ward patient

- **Beta lactam/ BLI** (ampicillin/ sulbactam or piperacillin/ tazobactam or amoxicillin/ clavulanic acid) plus a **macrolide**.

Treatment of patient requiring ICU admission

- A macrolide or a respiratory FQ plus either:
  - An extended spectrum cephalosporin e.g. ceftriaxone or cefotaxime OR
  - A beta lactam/ beta lactamase inhibitor (BLI)

Other considerations in treatment of hospitalized patients

- Treatment of a patient with penicillin allergies
  - Resp. FQ ± clindamycin
- Patients with suspected aspiration pneumonia should receive either:
  - A resp. FQ ± clindamycin
  - Metronidazole
  - A beta – lactam/ BLI

Cont.

- Patients with structural lung disease such as bronchiectasis or cystic fibrosis benefit from empiric therapy with the following until sputum culture & sensitivity results are available (cover known causes of pneumonia + an ***adequate gram negative cover***)
  - An antipseudomonal penicillin, carbapenem or cefepime plus
  - A resp. FQ

Cont.

- Almost all patient who are admitted in hospital for treatment of CAP should receive IV antibiotics.
- Duration of antibiotic treatment is the same as for the outpatients with CAP.

Prevention of CAP

- The main preventive measure is **vaccination:**
  - Polyvalent pneumococcal vaccine has the potential to prevent or lessen the severity of majority of pneumococcal infections in immunocompetent patients [Synflorix (PCV10), Prevenor (PCV 13)]
    - These are not given in adults unless in ISS, splenectomy, diabetics, asthmatics, old age etc. These are however ***recommended for all children***.

Cont.

- Haemophilus influenza type b (Hib) vax [single or in penta/ hexa vax]
- The influenza vaccine is effective in preventing severe disease due to influenza virus with a resulting +ve impact on both primary influenza pneumonia & secondary bacterial pneumonias.

SUMMARY OF CAP MANAGEMENT

Outpatient treatment

- **Mild CAP**: Amoxicillin PO 500mg 8hrly.
- **Other options if prev. healthy + no ABs in past 3/12**: Macrolides; Doxycycline 100mg PO BD; FQ; Amoxicillin - Potassium Clavulanate; Cephalosporins
- **Options if has comorbidities + ABs in past 3/12**: respiratory FQ, BL + Macrolide; cephalosporin

Treatment of hospitalized patients

- **Medical ward**: ESBL + Macrolide; Respiratory FQ; BL/BLI + Macrolide
- **ICU**:
  - Macrolide/ respiratory FQ + (ES cephalosporin/ BL/BLI)
  - Penicillin allergies → Resp. FQ ± clindamycin
  - ?Aspiration pneumonia → Resp. FQ ± Clindamycin/ Metronidazole/ BL/BLI
  - Structural lung disease → Antipseudomonal penicillin/ carbapenem/ cefepime + resp. FQ

2. HEALTH CARE ASSOCIATED PNEUMONIA (HCAP)

- Essentials of diagnosis
  - Definition: pneumonia developing >48hrs after admission to the hospital & excludes any infection present at the time of admission
  - At least 2 of the following:
    - Fever
    - Cough
    - Leukocytosis
    - *Purulent sputum*

Cont.

- New or progressive parenchymal infiltrate on CXR.
- The highest – risk patients are those requiring ICU care or mechanical ventilation.
  - However, majority of cases occur in patients who are not in the ICU.

General considerations

- HCAP is the 2nd MCC of infection among hospitalized patients & is the leading cause of death due to nosocomial infection with mortality rates ranging from 20 – 50%.

Pathogenesis

- *Colonization of pharynx & possibly the stomach with bacteria* is the most important step in the pathogenesis of HCAP.
- Pharyngeal colonization can be promoted by:
  - Exogenous factors
  - Patient factors

Exogenous factors include

- *Instrumentation* of the upper airway with nasogastric & endotracheal tubes
- *Contamination* by dirty hands and equipment &
- *Treatment with broad – spectrum antibiotics (BSAs)* that promote the emergence of drug – resistant organism.

Patient factors include

- Malnutrition
- Advanced age
- Altered consciousness
- Swallowing disorders
- Underlying pulmonary & systemic diseases

Cont.

- *Aspiration* of infected pharyngeal or gastric secretions delivers bacteria directly to the lower airway.
- *Impaired cellular and mechanical defense mechanisms* in the lungs of hospitalized patients raises the risk of infection after aspiration has occurred.

The role of the stomach in the pathogenesis of HCAP

- ↑ of gastric pH due to antacids, H_2 Receptor antagonists, PPIs or enteral feeding is associated with gastric microbial overgrowth, tracheobronchial colonization & HCAP.
- Sucralfate a cytoprotective agent that does not alter gastric pH is associated with a lower incidence of Ventilator Associated Pneumonia (VAP).

The MC organisms responsible for HCAP

- *P. aeruginosa*
- *S. aureus*
- *Enterobacter*
- *E. coli*
- *Klebsiella pneumonia*
- *Proteus, Serratia marcescens, H. influenzae* & *Streptococci* account for most of the remaining cases

Other causes

- Anaerobic organisms
  - *Bacteroides*
  - Anaerobic *streptococci*
  - *Fusobacterium*
- Mycobacteria, fungi, chlamydia, viruses, rickettsiae & protozoal organisms are uncommon causes of HCAP

Treatment of HCAP

- Empiric therapy for mild – moderate HCAP in a patient without unusual risk factors or a patient with severe early – onset HCAP (within 5 days after hospitalization) may consist of:
  - A 2nd generation cephalosporin
  - An antipseudomonal 3rd generation cephalosporin OR
  - A combination of a beta lactam & BLI e.g. amoxyclav

Cont.

- Empiric therapy for patients with severe late onset HCAP (occurs 5 or more days after hospitalization) or with ICU or VAP should include a combination of antibiotics directed against the most virulent organisms, particularly:
  - *P. aeruginosa*
  - *Acinetobacter spp.*
  - *Enterobacter spp.*

Cont.

- The antibiotic regimen should include an **aminoglycoside** or **FQ** plus one of the following:
  - An antipseudomonal penicillin e.g. piperacillin
  - An antipseudomonal cephalosporin e.g. ceftazidime
  - A carbapenem e.g. Meropenem

Cont.

- **Vancomycin** is added if infection with MRSA is of concern, esp. in patient with:
  - Coma
  - Head trauma
  - DM
  - Renal failure
  - Patients in ICU

Cont.

- Anaerobic coverage with clindamycin or a beta lactam/ BLI combination may be added for patients who have risk factors for anaerobic pneumonia including:
  - Aspiration
  - Recent thoracoabdominal surgery
  - An obstructing airway lesion

Cont.

- A **macrolide** is added when patients are at risk of Legionella infection such as those receiving high dose corticosteroids
- After results of sputum, blood & pleural fluid cultures have been obtained it may be possible to switch to a regimen with a narrow spectrum
- Duration of antibiotic treatment should be individualized based on:
  - Pathogen, severity of illness, response to therapy, comorbid conditions
- Treatment of gram –ve bacterial pneumonia should continue for at least 14 – 21 days.

Pulmonary infiltrates in the immunocompromised host

- These may arise infectious or non – infectious causes.
- Infection may be due to:
  - Bacterial
  - Mycobacterial
  - Fungal
  - Protozoal
  - Helminthic
  - Viral pathogens

Cont.

- Non – infectious processes
  - Pulmonary edema
  - Alveolar hemorrhage
  - Drug reactions
  - Pulmonary thromboembolic disease
  - Malignancy
  - Radiation pneumonitis
  - NB: these may mimic infection

RX OF THE IMMUNOCOMPROMISED HOST

- The evaluation & management of pulmonary infiltrates differs in the immunocompetent & immunocompromised hosts.
- Immunocompromised hosts are defined as patients with:
  - HIV disease
  - Absolute neutrophil counts <1000/mCL
  - Current or recent exposure to myelosuppressive or immunosuppressive drugs or those currently taking prednisone in a dosage of over 5mg/d

Cont.

- Although almost any pathogen can cause pneumonia in a compromised host, 2 clinical tools help the clinician narrow the differential diagnosis.
  - Knowledge of the underlying immunologic defect
  - The time course of infection

Significance of underlying immunologic defect

- Specific immunologic defects are associated with particular infections as follows:
  - Defects in *humoral immunity* predispose to **bacterial infections**
  - Defects in *cellular immunity* lead to infections with **viruses, fungi, mycobacteria & protozoa**
  - *Neutropenia and impaired granulocyte function* predispose to infections from *S. aureus*, Aspergillus, gram –ve bacilli & candida

The time course of infection

- A fulminant pneumonia is often caused by bacterial infection, whereas an insidious pneumonia is more likely to be caused by viral, fungal, protozoal or mycobacterial infection.
- Pneumonia occurring within 2 – 4 weeks after organ transplantation is usually bacterial, whereas several months or more after transplantation *P. jirovecii*, viruses (e.g. CMV) & fungi (e.g. Aspergillus) are more likely.

2. TREATMENT OF TUBERCULOSIS 15/2/2019

BY: DR. MUASYA

TYPED BY NAILA KAMADI

Definition

- TB is an infectious disease caused by Mycobacterium tuberculosis an Acid Fast Bacilli.
- Occasionally, it can be caused by *Mycobacterium bovis* which is transmitted through contaminated milk as well as by *Mycobacterium africanus*.

Transmission

- This occurs from person to person through aerosolized droplet nuclei.
- Coughing which generates infectious droplets is the most important mode of transmission.

Cont.

- An infectious patient is a person with a +ve sputum smear; a patient with miliary TB may not have a +ve sputum smear.
- In the majority infected with TB bacilli, the immune system contains the infection, the bacilli remain dormant for the rest of the person's life & they do not lead to disease.
- Reactivation occurs with ISS.
  - The rate of TB – HIV coinfection is 40% in our setup

Classification

- TB is classified as PTB & EPTB based on the site of disease.
- It is also classified according to:
  - Severity of disease
  - Treatment history
  - Drug resistant
- There is:
  - Non – severe TB
  - Severe TB
  - Retreatment TB
  - Multi – Drug Resistant TB (MDRTB)

Challenges in treatment of TB

- Mycobacterial infections are difficult to cure because:
  - They show **slow response** to treatment
  - They have a **tendency to develop resistance** to any single drug hence monotherapy is discouraged.

How to overcome these problems

- Drugs must be administered for months up to yrs. depending on the drug combinations used:
  - MDR TB is typically treated for up to 18 months.
- Use multiple drugs taken in combination to prevent emergence of drug resistance to any of the drugs during the course of treatment.

Aims of treatment

- Interrupt TB transmission by rendering patient non – infectious.
- Prevent morbidity & death by curing the patient with TB.

Drugs used in treatment of TB

- First line/ primary drugs
  - Isoniazid (H)
  - Pyrazinamide (Z)
  - Rifampin (R)
  - Ethambutol (E)
  - Streptomycin (S)
- 2nd line/ alternative drugs

1st line drugs are classified as:

- Essential drugs
- Supplemental drugs

Essential 1st line drugs

- These are the MOST effective anti – TB drugs.
- They are a necessary component of **Short Course Chemotherapy (SCC)**
- They include:
  - INH
  - Rifampin
  - Pyrazinamide
  - Ethambutol
- INH & rifampin are the 2 most active drugs.

Supplemental 1st line drugs

- These are highly effective and with acceptable toxicity.
- They include:
  - Streptomycin
  - Long acting Rifamycin derivatives:
    - Rifabutin
    - Rifapentine

2nd line anti – TB drugs

- These have a ***lower degree of efficacy*** & a ***higher degree of intolerability & toxicity*** compared to the 1st line drugs.
- They are rarely used.
- They should be considered in the following circumstances:
  - When expert guidance is available to deal with their toxic effects.
  - Patients with treatment failure or TB that is resistant to first line drugs.
  - When first line supplemental drugs are not available.
  - In case of serious Rx – limiting ADR to 1st line drugs
- For many of the 2nd line drugs, the dosage, emergence of resistance & long term toxicities have not been well established.

Cont.

- The 2nd line anti – TB drugs are listed in descending order of usefulness as follows:
  - FQ antibiotics: 3rd generation agents are preferred
    - **Moxifloxacin** (most active against MTB), levofloxacin, ciprofloxacin & gatifloxacin
  - Capreomycin, a complex cyclic polypeptide AB (injectable)

Cont.

- Aminoglycosides: amikacin is less toxic than kanamycin (injectable).
- Ethionamide (prothionamide) → PO
- Para – aminosalicylic acid – PAS → PO
- Cycloserine → PO
- Linezolid

Drug regimens used for Rx of TB

- An R/H combination administered for 9 months cures 95 – 98% of TB caused by susceptible strains.
- The addition of Z to RH for the 1st 2 months (2RHZ/4RH) allows the total duration of treatment to be ↓ to 6/12 without loss of efficacy.

SCC regimens

- They are currently recommended by WHO for Rx of all TB patients & have been adopted by Kenya National TB, Leprosy & Lung Disease Program.
- SCC regimens are divided into 2 phases:
  1. An initial/ intensive/ bactericidal phase → 1st 2 months of RX
  2. A continuation/ sterilizing phase → the subsequent 4 – 6 months of Rx.

Cont.

- During initial phase:
  - Majority of TB bacilli are killed hence the term bactericidal phase.
  - Symptoms resolve
  - The patient usually becomes non – infectious
  - Incase of a + sputum microscopy test at the end of the initial phase, prolong this phase by a month.
- The continuation phase is required to eliminate persisting mycobacteria & to prevent relapse.

Cont.

- The Rx regimen of choice for virtually all forms of TB in both adults & children consists of:
  - A 2 month – initial phase of R/H/Z/E followed by
  - A 4 month continuation phase of R/H
- i.e. 2RHZE/ 4 RH

Cont.

- R/H/Z/E are:
  - Well absorbed after oral administration
  - Their peak serum levels occur at 2 – 4 h
  - They have nearly complete elimination within 24h

Cont.

- These drugs are recommended on the basis of:
  - Bactericidal activity (i.e. their ability to rapidly ↓ the number of viable organisms & render patients non – infectious)
  - Their sterilizing activity (i.e. their ability to kill all bacilli and thus sterilize the affected tissues, measured in terms of the ability to prevent relapse)
  - Their low rate of induction of drug resistance

Cont.

- Rx may be given
  - Daily throughout the course of treatment (preferred)
  - Intermittently 3 times a week throughout the course
    - Esp. useful for patients whose therapy is being directly observed (DOTS = directly observed therapy short course)
    - May be used in the nomadic populations

Cont.

- Patients with cavitatory PTB and delayed sputum culture conversion (i.e. those who remain culture +ve at 2 months) *should have the continuation phase extended by 3 months for a total course of 9 months. – confirm this with latest guidelines & with TB specialist Dr. Mecha.*
- To prevent INH – related neuropathy, **pyridoxine** (10 – 25 mg/d) should be added to the regimen given to persons at a high risk of Vit. B_6 deficiency:
  - Alcoholics
  - Malnourished persons
  - Pregnant & lactating women
  - Patients with conditions such as: chronic renal failure, DM, HIV infection, which are also associated with neuropathy

WHO TB treatment guidelines 2013

- All forms of PTB & EPTB except TBM & osteoarticular TB:
  - Intensive: 2HRZE
  - Continuation: 4HR
- TBM & osteoarticular TB
  - Intensive: 2HRZE
  - Continuation: 10HR
- **Retreatment
  - Intensive: 3RHZE
  - 5HRE
- Drug resistant TB: Refer to a DRTB specialist

Impediments to cure

- **Lack of adherence** to Rx is the most important impediment to cure worldwide. Adherence counselling is important before initiating treatment.
- In addition, the TB bacilli infecting patients who do not adhere to the prescribed regimen are likely to become **drug resistant**

Cont.

- In addition to specific measures which address non – compliance, there are 2 other strategies that are used:
  1. DOTs
  2. Provision of fixed drug combination products
     - Currently most anti – TB drugs are available as tablets containing multiple drugs in Fixed Dose Combinations (FDCs)

Cont.

- It is difficult to predict which patients will adhere to recommended treatment
  - Therefore all patients should have their therapy directly supervised esp. during the initial phase
- Supervision increases the proportion of patients completing Rx & greatly lessens the chances of relapse and acquiring drug resistance.

FDC products available in Kenya

- H/R: Rifina
- H/R/Z: Rifater
- H/R/Z/E: Rifafour

Cont.

- FDCs are strongly recommended as a means of minimizing the likelihood of prescription error & of the development of drug resistance as a result of monotherapy
- Alternative regimens for patients who demonstrate drug intolerance or adverse reactions are available
- However severe A/Es prompting discontinuation of any of the 1st line drugs & use of these alternative regimens are uncommon

Rx of TB in pregnancy

- In general pregnancy should be avoided during anti – TB treatment
- H/R/Z/E & rifapentine are classified under FDA category C (risk cannot be R/O in pregnancy)
  - Remember rifampin is an inducer of contraceptive metabolism hence, if administering contraceptives, you may need to use higher doses.
- Rifabutin is FDA category B (no evidence of risk)
- Give pyridoxine with INH to avoid the risk of damaging the infant's nervous system.

Cont.

- Streptomycin should not be used in pregnancy as it may cause deafness in the infant.
- The following should not be used for treatment of DRTB in pregnancy (as they are classified as FDA category D → definite evidence of risk)
  - Aminoglycosides
  - Capreomycin
  - Thioamides e.g. Ethionamide

Rx of TB in children

- Children usually have paucibacillary (low organism numbers) pulmonary disease & cavitatory disease is rare (majority of the organisms in adult – type disease are found in the cavities) &
- EPTB is common among children.
- R/O ISS or malnutrition
- Severe & disseminated TB (e.g. miliary TB & TBM) occurs esp. in
  - Young children < 4 yrs.
  - HIV infected children

Cont.

- Rx outcomes are generally good even in the HIV infected provided Rx is started promptly
- Children require an adult to supervise them
- Children generally tolerate the anti – TB drugs better than adults.

Rx of adolescents & adult patients with HIV coinfection

- To be covered in a separate lecture of Rx of OIs.

Rx of DRTB

- There are various categories of TB resistance:
  1. Mono resistance when there is resistance to any one single anti – TB drug.
  2. Poly – drug resistant (PDR) resistance to 2 or more anti – TB drugs ***but excluding R & H***.
  3. MDR TB when there is resistance to both R & H.

Cont.

- Extensively (X) DRTB
  - Documented MDR TB +
  - Resistance to a quinolone & at least one injectable
    - Kanamycin
    - Amikacin
    - Capreomycin
- Resistance beyond XDRTB

The major reasons for developing DRTB

- Kenya receives a large population of refugees from the surrounding countries where there has been ongoing civil strife
- ***Find out other reasons.***

Rx of MDR – TB (Kenya Treatment Guidelines 2013)

- 2 phases
  - Intensive phase of 8 months
  - Continuation phase of 12 months

Intensive phase – 8 Km – Pto – Lfx – Cs – Z

- This lasts for a minimum of 8 months & the following drugs are used:
  - Inj. Kanamycin (Km)
  - Tabs Prothionamide (Pto)
  - Tabs Levofloxacin (Lfx)
  - Tabs Cycloserine (Cs)
  - Tabs Pyrazinamide (Z)

Continuation phase – 12 Pto – Lfx – Cs – Z

- This lasts for 12 months and uses the following drugs:
  - Tabs prothionamide
  - Tabs Levofloxacin
  - Tabs Cycloserine
  - Tabs Pyrazinamide

ADR to anti – TB drugs

- During Rx patients should be monitored for drug toxicity; ensure you inform the patient the signs of toxicities for which they should return to hospital.
- The most common ADR of significance is **hepatitis**
  - Ethambutol, Rifabutin & streptomycin require no dose adjustment in hepatic disease.
  - Avoid the use of the following in severe hepatic disease or monitor carefully: H, Z, R & rifapentine
  - Incidence of hepatotoxicity: Pyrazinamide > INH > Rifampin

Cont.

- **Hypersensitivity reactions** usually require discontinuation of all drugs & a re – challenge to determine which drug is the culprit.
- **Hyperuricemia** & **arthralgia** caused by **pyrazinamide** can usually be managed by the administration of ASA.
  - However, pyrazinamide Rx should be stopped if the patient develops **gouty arthritis**

Cont.

- Individuals who develop **autoimmune thrombocytopenia** secondary to **rifampin** treatment should not receive the drug thereafter.
- The occurrence of **optic neuritis** with **ethambutol** is also an indication for permanent discontinuation of this drug.
- Other common manifestations of drug intolerance such as **pruritus** & **GIT upset** can generally be managed without the interruption of Rx.

Cont.

- **Renal impairment**
  - Ethambutol, Isoniazid, Rifampin, Rifabutin & Rifapentine do not require dosage adjustment in renal failure.
  - ↓ dose of Pyrazinamide in severe renal impairment (creatinine clearance rate < 30mL/min)
  - ↓ dose of streptomycin at creatinine clearance rate < 60 but > 30 mL/min.
    - ↓ its dose and frequency at creatinine clearance < 30mL/min

Read about

- Ways of preventing MDRTB

Further Reading Material

- https://www.nltp.co.ke.guidelines/
- Go to Resources → drop down menu on Guidelines → Download NTLD – PTB treatment guidelines → Page 60

3. MANAGEMENT OF CHRONIC OBSTRUCTIVE AIRWAY DISEASE

1st/3/2019

BY: DR. GICHUHI

TYPED BY NAILA KAMADI

Introduction

- Characterized by persistent respiratory symptoms & airflow limitation
- These are due to airway/ alveolar abnormalities
- Chronic airflow limitation is caused by a mixture of
  - Small airway disease (e.g. obstructive bronchiolitis) & parenchymal destruction (emphysema)

Risk factors

- Noxious gases + host factors combined
- Noxious gases
  - Tobacco smoking
  - Marijuana
  - Air pollution
    - Outdoor
    - Occupational
    - Indoor burning of biomass fuels e.g. wood

Host factors

- Genetics
- Airway hyper responsiveness
- Poor lung growth during childhood

COPD should be considered in any patient who has:

- Dyspnea, chronic cough or sputum production &/or
- History of exposure to risk factors for the disease

Cont.

- Spirometry is required to make the diagnosis
- The presence of a post – bronchodilator FEV_1/FVC ratio of <0.70 confirms the presence of persistent airflow limitation.
- Grading of COPD is based on **Global initiative for chronic Obstructive Lung Disease (GOLD) criteria**.

For management classify patient based on:

- Spirometry based airflow limitation (GOLD)
- Modified MRC dyspnea scale (mMRC)
- COPD assessment test (CAT)
- See reference for details

Assessment of airflow limitation

GOLD GRADE	FEV_1 (% PREDICTED)	
1	≥ 80%	Mild
2	50 – 79%	Moderate
3	30 – 49%	Severe
4	< 30%	Very Severe

Cont.

- Prediction values for FEV_1 are found in tables and they vary based on age, gender & race

Table 2.5. Modified MRC dyspnea scale[a]

PLEASE TICK IN THE BOX THAT APPLIES TO YOU (ONE BOX ONLY) (Grades 0–4)	
mMRC Grade 0. I only get breathless with strenuous exercise.	☐
mMRC Grade 1. I get short of breath when hurrying on the level or walking up a slight hill.	☐
mMRC Grade 2. I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.	☐
mMRC Grade 3. I stop for breath after walking about 100 meters or after a few minutes on the level.	☐
mMRC Grade 4. I am too breathless to leave the house or I am breathless when dressing or undressing.	☐

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Comprehensive assessment of symptoms

Figure 2.3. CAT Assessment

For each item below, place a mark (✗) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy (0) (✗) (2) (3) (4) (5) I am very sad

			SCORE
I never cough	0 1 2 3 4 5	I cough all the time	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	
I have lots of energy	0 1 2 3 4 5	I have no energy at all	

TOTAL SCORE

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Reference: Jones et al. ERJ 2009; 34 (3); 648-54.

Spirometrically confirmed diagnosis

Post-bronchodilator $FEV_1/FVC < 0.7$

Assessment of airflow limitation

	FEV_1 (% predicted)
GOLD 1	≥ 80
GOLD 2	50-79
GOLD 3	30-49
GOLD 4	< 30

Assessment of symptoms/risk of exacerbations

Exacerbation history

- ≥ 2 or ≥ 1 leading to hospital admission
- 0 or 1 (not leading to hospital admission)

C	D
A	B

mMRC 0–1 CAT < 10 | mMRC ≥ 2 CAT ≥ 10

Symptoms

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Example of classified patient

- GOLD grade 4, group D
- GOLD grade 4, group B

Management of stable COPD

- Goals
  - Reduce symptoms
    - Relieve symptoms
    - Improve exercise tolerance
    - Improve health status
  - Reduce risk
    - Prevent disease progression
    - Prevent & treat exacerbations
    - Reduce mortality

Cont.

- Reduction exposure to risk factors
  - For treatment and prevention of COPD
- Counsel on
  - Smoking cessation
  - Reduction of total personal exposure to
    - Occupational dusts, fumes & gases
    - Indoor air pollutants
    - Outdoor air pollutants

Tobacco smoke cessation

- Counselling
- Treatment of tobacco dependence
  - ***Varenicline***: partial agonist at nicotine receptors
  - ***Bupropion*** sustained release: partial agonist at opioid receptors
  - ***Nicotine gum***, ***inhaler***, ***spray*** or ***patch*** to aid the process

Cont.

- Efficient ventilation
- Non – polluting cooking stoves

Pharmacologic therapies can

- Reduce
  - Symptoms
  - The risk and severity of exacerbations
- Improve
  - Health status
  - Exercise tolerance

Group A

- Start a ***bronchodilator***
- Evaluate effect then,
- Continue, stop or try alternative class of bronchodilators.

Cont.

- Bronchodilator medications in COPD are most often given on regular basis to prevent or reduce symptoms.
- Use ***SABA (salbutamol)*** or ***SAMA or Long acting bronchodilators (LABD)***
- LABA
  - Formoterol & salmeterol BD
  - Indacaterol, Olodaterol & Vilanterol OD

Other bronchodilators

- SAMA: Ipratropium and Oxitropium
- LAMA
  - Tiotropium
  - Aclidinium
  - Glycopyrronium bromide
  - Umeclidinium

Adverse effects

- Inhaled anticholinergic drugs are poorly absorbed
- The main side effect is dryness of mouth

Group B

- Start with a long acting bronchodilator (LABA or LAMA)
- If symptoms persist → LAMA + LABA

Group C

- Start with LAMA
- If there are further exacerbations →
  - LAMA + LABA OR;
  - Go to LABA + ICS

Group D

- LAMA & LABA/ LABA & ICS
- If further exacerbations → LAMA + LABA + ICS
- If further exacerbations
  - Consider **roflumilast** if FEV_1 < 50% of predicted & patient has chronic bronchitis
  - Consider **macrolides** in former smokers

Roflumilast

- This is a PDE_4 inhibitor
- Adverse effects
  - Most frequent are in the GIT
  - Abdominal pain, nausea & diarrhea
  - Weight loss
  - Sleep disturbance
  - Headache

Antibiotics

- Regular use of macrolide antibiotics may reduce exacerbation rate.

Cont.

- In COPD patients not receiving ICS, regular treatment with mucolytics
  - E.g. carbocysteine
  - N – acetylcysteine
  - Erdosteine
- May reduce exacerbations and modestly improve health status

Prescription of supplemental O_2

- Arterial hypoxemia defined as
  - PaO_2 < 55mmHg (8 kPa) or SaO_2 < 88% or
  - PaO_2 > 55 but < 60mmHg (>8 but < 8.5 kPa) with RHF or erythrocytosis.

Cont.

- If one has hypoxemia prescribe supplemental O_2 and titrate to keep $SaO_2 \geq 90$.
- Recheck in 60 – 90 days to asses;
  - If oxygen is still indicated
  - If prescribed supplemental oxygen is effective

Cont.

- Influenza vaccine for all COPD
- Pneumococcal vaccine
  - > 65 yrs.
  - Younger patients with significant comorbidities e.g. chronic heart disease.
- Offer nutritional support if the patient is malnourished.

Cont.

- If chronic hypercapnia and a history of acute respiratory failure then non – invasive ventilation using a nasal catheter or mask is considered.

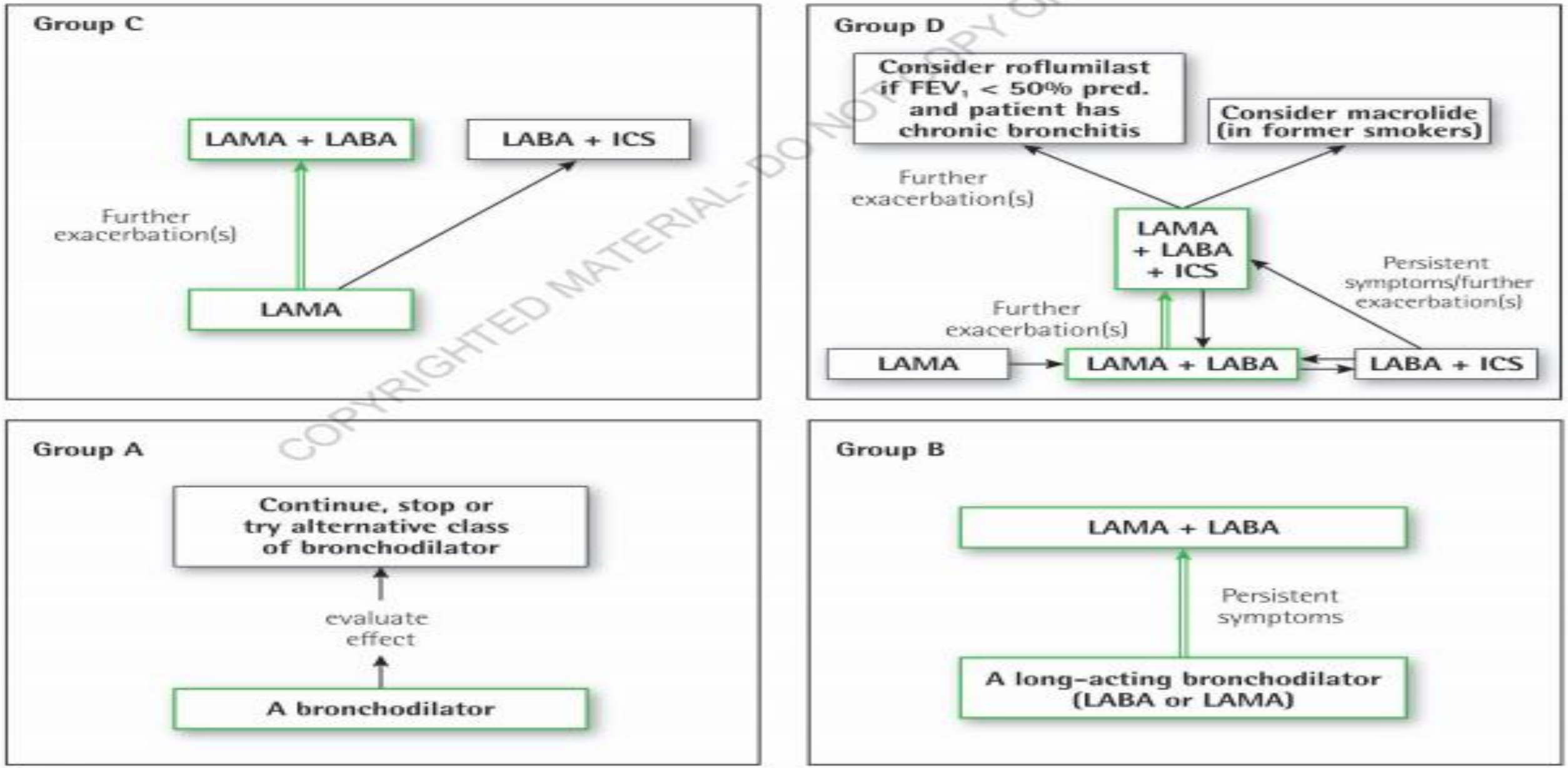
Cont.

- Surgery & bronchoscopy may be useful for:
  - Reducing lung volume in emphysema
  - Bullectomy in patients with large bulla
  - Lung transplant

Cont.

- Routine follow up of COPD patients is essential
  - Lung function may worsen over time
- Monitor
  - Symptoms, exacerbations and objective measures of airflow limitation
  - Determines when to modify management

Figure 4.1. Pharmacologic treatment algorithms by GOLD Grade [highlighted boxes and arrows indicate preferred treatment pathways]



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Preferred treatment ⟶

In patients with a major discrepancy between the perceived level of symptoms and severity of airflow limitation, further evaluation is warranted.

Management of exacerbations

- An exacerbation of COPD is defined as an acute worsening of respiratory symptoms that results in additional therapy.
- Exacerbations of COPD can be precipitated by several factors
  - The MCC are RTIs.

Goal of treatment of COPD exacerbations

- Minimize negative impact of the current exacerbation on the lung.
- To prevent subsequent events.

COPD exacerbations classified according to what was needed to control

- Mild: treated with SABA only, SABDs.
- Moderate: treated with SABD + antibiotics ± OCS
- Severe: patient requires hospitalization or visits the emergency room.
  - May also be associated with acute respiratory failure

Cont.

- Exacerbations are characterized by increased dyspnea as a key symptom.
- Other symptoms
  - Increased
    - Sputum purulence and volume
    - Cough and wheeze

The 3 classes of medications MC used for exacerbations

- Bronchodilators (BDs)
- Corticosteroids (Cs)
- Antibiotics (ABs)

Cont.

- Inhaled SABA ± SAMA are recommended as the initial BD to Rx an acute exacerbation.
- Maintenance therapy with LABD should be initiated asap.

Systemic Corticosteroids

- Can improve
  - Lung function (FEV_1)
  - Oxygenation
  - Shorten recovery time and hospitalization
- Duration of therapy should not be more than 5 – 7 days

Cont.

- If antibiotics are indicated
- Duration of therapy should be 5 – 7 days
- Methylxanthines are not recommended due to increased side effect profiles
  - Always remember aminophylline is administered slowly over 15 min

Cont.

- Non invasive mechanical ventilation
  - By nasal tubes or face mask
- Monitor fluid balance
- Thromboembolism prophylaxis
  - LMWH

Reference

https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-POCKET-GUIDE-DRAFT-v1.7-14Nov2018-WMS.pdf

When feeling overwhelmed by a far away goal, repeat the following, “I have it within me right now to get me to where I want to be later. If it is to be, it is up to me.”

- Karen Salmansohn

#I_Can_Do_All_Things_Through_Christ_Who_Strengthens_Me

4. MANAGEMENT OF BRONCHIAL ASTHMA

21/2/2019

BY: DR. GICHUHI

TYPED BY NAILA KAMADI

Objectives

- Introduction
- Risk factors for asthmatic attacks
- Risk factors for drug adverse effects
- Goals of long term treatment
- Classification of drugs
- Levels of asthma control
- 5 steps of drug management
- Treatment of an acute asthmatic attack
- Drug adverse effects

Introduction

- Asthma is a ***chronic inflammatory airway disease*** encompassing ***airway hyper – responsiveness (AHR)***.
- Airflow is limited due to:
  1. Bronchoconstriction
  2. Mucus plugs
  3. Inflammation
- **Airway inflammation** is chronically present.
- Asthma attacks are **episodic/ paroxysmal.**

Diagnosis of asthma

19.21 How to make a diagnosis of asthma

Compatible clinical history *plus either/or*:

- $FEV_1 \geq 15\%$* (and 200 mL) increase following administration of a bronchodilator/trial of corticosteroids
- > 20% diurnal variation on ≥ 3 days in a week for 2 weeks on PEF diary
- $FEV_1 \geq 15\%$ decrease after 6 mins of exercise

*Global Initiative for Asthma (GINA) definition accepts an increase of 12%.

Risk factors for future exacerbations

- A history of a an acute, severe asthmatic attack that ***required intubation***.
  - ***Indications for assisted ventilation in acute severe asthma:***
    1. Exhaustion, confusion & drowsiness
    2. Coma
    3. Respiratory arrest
    4. Deterioration of ABG tensions despite optimal therapy: PaO2 < 60mmHg & falling; PaCO2 > 45mmHg & rising; pH low & falling.

Cont.

- Uncontrolled asthma symptoms.
- Having ≥ 1 ***exacerbation*** (***increased symptoms, deterioration in lung function & increase in airway inflammation***) in the last 12 months.
- $FEV_1 < 60\%$
- Not using regular 'preventer' therapy preferably Inhaled Corticosteroids (ICS) e.g. *budesonide*, *beclometasone*, *fluticasone*, *ciclesonide*
  - NB: Regular therapy with low – dose budesonide reduces the risk of severe exacerbations in patients with mild persistent asthma.

Cont.

- Incorrect inhaler technique
- Poor adherence.
- High Short Acting β_2 Agonist (SABA) use (> 1 X 200 dose canister/ month)
- Exposures to modifiable triggers of attacks: smoking, allergens, pets
- Major psychological (depression, anxiety) or socioeconomic problems

Cont.

- Comorbidities: obesity, rhinosinusitis, food allergy
- Pregnancy
- Blood or sputum eosinophilia

Risk factors for drug A/Es

- High dose ICS
- Frequent Oral Corticosteroid (OCS) use
  - Patients on long term OCS (> 3 months) or receiving > 3 – 4 courses per year will be at risk of systemic side effects. Osteoporosis can be prevented in this group by using ***bisphosphonates***. **Steroid sparing therapies include: MTX, cyclosporine, oral gold, Omalizumab**.
- Use along with CYP450 inhibitors

Goals of long term management

- Achieve & maintain ***symptom control***.
- Maintain:
  - Normal ***activity levels*** (including exercise)
  - ***Pulmonary functio***n as close to normal levels as possible.
- Avoid ***adverse effects*** from asthma medications.
- ***Prevent***:
  - Asthmatic ***exacerbations***
  - Asthma ***mortality***.

Classification of drugs: Quick Relief Drugs

- Adrenergic receptor agonists:
  - Short – Acting β_2 Agonists (SABAs): inhaled, oral
  - ***Epinephrine***
- Short Acting Muscarinic Antagonists (SAMAs): ***Ipratropium bromide***, ***Oxitropium***
- Methylxanthines

Long Term Controller Drugs

- Corticosteroids: inhaled, systemic
- Long Acting β_2 Agonist (LABA) + ICS
- Mast cell stabilizing agents: ***chromones***
- Leukotriene Receptor Blockers (LTRB)
- Omalizumab

Cont.

- Long Acting Muscarinic Antagonists (LAMAs): ***tiotropium***
- Anti – IL5 antibodies: ***SC mepolizumab, IV reslizumab***
- Sustained release tablets: ***Salbutamol, terbutaline, aminophylline***

Reliever medication

- Used on an as – required basis (PRN) for patients with ***mild intermittent asthma*** (*symptoms < once per week for 3 months & < 2 nocturnal episodes/ month*)
- Occasionally required to ***treat acute attacks***.

Controller medication

- May be taken daily.
- Prevent:
  - Symptoms.
  - Severe attacks/ exacerbations
- Improve lung function

Levels of asthma control: Determined by taking a history of the ***past 4 weeks***

19.22 Levels of asthma control*

Characteristic	Controlled	Partly controlled (any present in any week)	Uncontrolled
Daytime symptoms	None (≤ twice/wk)	> twice/wk	≥ 3 features of partly controlled asthma present in any wk
Limitations of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for rescue/'reliever' treatment	None (≤ twice/wk)	> twice/wk	
Lung function (PEF or FEV_1)	Normal	< 80% predicted or personal best (if known) on any day	
Exacerbation	None	≥ 1/yr	1 in any wk

*Based on GINA guidelines.

Cont.

Well controlled (all of the following)

- Day time symptoms (none or ≤ 2 times/ week)
- No limitation of activity
- No nocturnal symptoms/ awakening due to coughing or wheezing
- Need for reliever (none or ≤ 2 times a week).

Cont.

Partly controlled (1 – 2 of the following)

- Day time symptoms > twice/wk.
- Any limitation of activity
- Any nocturnal symptoms/ awakening due to coughing or wheezing
- Need for a reliever > twice a week

Uncontrolled

- 3 – 4 features listed for partially controlled asthma.

Asthma management: Patient education

- ***Avoidance strategies***: remove or reduce exposure to relevant antigens e.g. pets, replacing carpets with floor boards, using mite impermeable bedding, avoiding medications known to precipitate or aggravate asthma, smoking cessation (*smoking encourages sensitization & induces a relative steroid resistance in the airway*)
  - Many patients are sensitized to several ubiquitous aeroallergens, making avoidance strategies largely impractical.

Cont.

- Correct intake of medications: Understanding the difference between the controller & reliever medications.
- Recognizing that asthma is worsening & taking action.
- Seeking medical help as appropriate

Cont.

- Identifying & reducing exposure to risk factors if possible:
  - House dust mites
    - No carpet
    - Wash bed linens & blankets weekly in hot water & dry in the sun
    - Pillows and mattresses: use air tight covers

Cont.

- ***Patients should not avoid exercise!***
  - The following can protect against exercise – induced symptoms:
    - Adequate warm up exercise
    - Pre – treatment with:
      - Inhaled SABA
      - Nedocromil sodium
      - LTRB e.g. montelukast sodium

Teach patients how to use an MDI

- Remove the cap and shake the inhaler
- Breathe out gently and place the mouthpiece into the mouth
- Incline the head backwards to minimise oropharyngeal deposition
- Simultaneously, begin a slow deep inspiration, depress the canister and continue to inhale
- Hold the breath for 10 seconds

Fig. 19.23 How to use a metered-dose inhaler.

Cont.

- Demonstrate for the patient.
- Administer illustrated instructions.
- Check technique at every visit.

Stepwise approach to the management of asthma is based on:

- Efficacy
- Safety
- Cost

Patients should start treatment at the step most appropriate to the initial severity of their asthma. Check concordance and reconsider diagnosis if response due to treatment is unexpectedly poor

Move up to improve control as needed

Move down to find and maintain lowest controlling step

Inhaled short-acting β_2-agonist as required

STEP 1

Mild intermittent asthma

Add inhaled steroid 200–800 µg/day*

400 µg is an appropriate starting dose for many patients

Start at dose of inhaled steroid appropriate to severity of disease

STEP 2

Regular preventer therapy

1 Add inhaled long-acting β_2-agonist (LABA)

2 Assess control of asthma:

- **Good response to LABA**
  – continue LABA
- **Benefit from LABA but control still inadequate**
  – continue LABA and increase inhaled steroid dose to 800 µg/day* (if not already on this dose)
- **No response to LABA**
  – stop LABA and increase inhaled steroid to 800 µg/day.* If control still inadequate, institute trial of other therapies, leukotriene receptor antagonist or SR theophylline

STEP 3

Initial add-on therapy

Consider trials of:

- Increasing inhaled steroid up to 2000 µg/day*
- Addition of a fourth drug, e.g. leukotriene receptor antagonist, SR theophylline, β_2-agonist tablet

STEP 4

Persistent poor control

Use daily steroid tablet in lowest dose providing adequate control

Maintain high-dose inhaled steroid at 2000 µg/day*

Consider other treatments to minimise use of steroid tablets

Refer patient for specialist care

STEP 5

Continuous or frequent use of oral steroids

Symptoms vs **Treatment**

Fig. 19.22 Management approach in adults based on asthma control. *Beclometasone dipropionate (BDP) or equivalent. From British Thoracic Society and SIGN — see p. 732.

Step 1: Occasional use of inhaled SABA

- Indication: mild, intermittent asthma (*symptoms < once per week for 3 months & < 2 nocturnal episodes/ month*)
- Reliever: ***SABA as needed (PRN)***
- Controller: none (Consider low dose ICS)

Indications of stepping up:

- Experiencing an exacerbation in the last 2 yrs.
- Reporting symptoms ≥ 3 times in a week.
- Using inhaled SABA ≥ 3 times in a week.
- Nocturnal symptoms/ awakening in a night per week.

NOTE!

REFER TO GINA 2019 RECOMMENDATIONS FOR FURTHER STUDY

A MAJOR CHANGE IN GINA 2019 RECOMMENDATIONS FOR MILD ASTHMA

From 2019, for safety, GINA no longer recommends starting with SABA-only treatment. GINA recommends that all adults and adolescents with asthma should receive ICS-containing controller treatment, to reduce their risk of serious exacerbations and to control symptoms.

Box 7 (p.18) shows the new ICS controller options. These now include:

- (for mild asthma) as-needed low dose ICS-formoterol*, or if not available, low dose ICS taken whenever SABA is taken†, or
- regular ICS or ICS-LABA every day, plus as-needed SABA, or
- maintenance and reliever treatment with ICS-formoterol, with the reliever being low-dose budesonide-formoterol or BDP-formoterol.

*Off-label; evidence only with budesonide-formoterol; †Off-label, combination or separate inhalers. For ICS dose ranges, see Box 8, p.20.

Step 2: introduction of regular ‘preventer’ therapy

- Reliever: SABA PRN
- Controller
  - Low dose ICS (***preferred choice***)
    - In an adult a reasonable starting dose is ***400mcg beclomethasone dipropionate (BDP) or equivalent per day***.
    - Higher doses may be required in smokers.
  - Alternative but much less effective preventive agents include: ***LTRBs, theophyllines, chromones***

Step 3: Add – on therapy

- Indication: patient remains poorly controlled despite regular, appropriately dosed ICS (800 mcg/d).
- Patient education with a focus on:
  - Adherence
  - Inhaler technique
  - On – going exposure to modifiable aggravating factors.

Cont.

- Reliever
  - ***Inhaled SABA PRN*** or
  - ***Low dose ICS + LABA*** (formoterol/ salmeterol; considered for both maintenance & reliever therapy)
    - LABA have consistently been demonstrated to improve asthma control & reduce frequency and severity of exacerbations when compared to increase ICS dose alone.

Cont.

- Controller
  - ***Low dose ICS + LABA (preferred)***
  - Other options:
    - Medium/ high dose ICS
    - Low dose ICS + theophylline or LTRA
- NB: ***LABA is not used as monotherapy!.***
  - Fixed combination inhalers of ICS & LABAs are more convenient. They increase compliance & prevent using a LABA as a monotherapy (***which may be accompanied by increased risk of life – threatening attacks or asthma death***)

Step 4: addition of 4th drug

- Indication: poor control on moderate dose of ICS & add – on therapy
- Reliever: Like step 2
- Controller: ***Medium/ high dose ICS + LABA*** (preferred)
  - In adults the dose of ICS may be increased to 2000mcg BDP/ budesonide (or equivalent) daily.

Cont.

- Other options
  - High dose ICS + LABA OR
  - Additional LAMA: ***tiotropium*** OR
  - Additional ***LTRB*** or slow release ***theophylline***
  - ***Oral itraconazole*** in patients with allergic bronchopulmonary aspergillosis (ABPA)

Step 5: continuous or frequent use of oral steroids

- ***Should be referred to an asthma specialist available!***
- Reliever: Like step 3
- Controller: Options to add to step 4 Rx
  - Oral CS: Prednisolone single, daily dose in the morning should be prescribed at the lowest dose (1mg/kg up to 60 mg/ day) needed to control symptoms.
  - LAMA: ***tiotropium***
  - Anti – IgE: ***Omalizumab***
  - Anti – IL – 5: SC ***mepolizumab***, IV ***reslizumab***

Box 7. The GINA asthma treatment strategy

Adults & adolescents 12+ years

Personalized asthma management:
Assess, Adjust, Review response

Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (including lung function)
Comorbidities
Inhaler technique & adherence
Patient goals

Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction

Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Education & skills training
Asthma medications

Asthma medication options:
Adjust treatment up and down for individual patient needs

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms	As-needed low dose ICS-formoterol *	Daily low dose inhaled corticosteroid (ICS), or as-needed low dose ICS-formoterol *	Low dose ICS-LABA	Medium dose ICS-LABA	High dose ICS-LABA Refer for phenotypic assessment ± add-on therapy, e.g. tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R
Other controller options	*Low dose ICS taken whenever SABA is taken †*	*Leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken †*	*Medium dose ICS, or low dose ICS+LTRA #*	*High dose ICS, add-on tiotropium, or add-on LTRA #*	*Add low dose OCS, but consider side-effects*
PREFERRED RELIEVER	As-needed low dose ICS-formoterol *		As-needed low dose ICS-formoterol ‡		
Other reliever option	*As-needed short-acting β_2-agonist (SABA)*				

* Off-label; data only with budesonide-formoterol (bud-form)
† Off-label; separate or combination ICS and SABA inhalers
‡ Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy
# Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV1 >70% predicted

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For children 6–11 years, the preferred Step 3 treatment is low dose ICS-LABA or medium dose ICS.

Severity of asthma

1. Mild asthma: well controlled at step 1 or 2
2. Moderate asthma: well controlled at step 3
3. Severe asthma: well controlled at step 4 or 5

Cont.

- If not well controlled
  - Check inhaler technique
  - Avoid risk factors
- Step up Rx until control is achieved
- ***If step 4 is not controlling well for 3 – 6 months, refer to a specialist***.

Step – down therapy

- If well – controlled for 3 months & low risk of exacerbations start stepping down Rx:
  - Find lowest controlling step
  - Reduce ICS dose by 25 – 50% every 2 – 3 months
  - ***Stopping low dose ICS is not advised as asthma is a chronic inflammatory disease***

Low, medium and high dose inhaled corticosteroids Adults and adolescents (≥12 years)

Inhaled corticosteroid	Total daily dose (mcg)		
	Low	Medium	High
Beclometasone dipropionate (CFC)	200–500	>500–1000	>1000
Beclometasone dipropionate (HFA)	100–200	>200–400	>400
Budesonide (DPI)	200–400	>400–800	>800
Ciclesonide (HFA)	80–160	>160–320	>320
Fluticasone propionate (DPI or HFA)	100–250	>250–500	>500
Mometasone furoate	110–220	>220–440	>440
Triamcinolone acetonide	400–1000	>1000–2000	>2000

- This is not a table of equivalence, but of estimated clinical comparability
- Most of the clinical benefit from ICS is seen at low doses
- High doses are arbitrary, but for most ICS are those that, with prolonged use, are associated with increased risk of systemic side-effects

Cont.

- CFC: chlorofluorocarbon propellant
- HFA: hydrofluoroalkane propellant
- DPI: dry powdered inhaler

Cont.

- Frequency of patient review
  - See patient 1 – 3 months after the initial visit
  - Every 3 – 12 months thereafter
- After an exacerbation: See patient within 1 week

Manage exacerbation

- ***Exacerbations of asthma (asthma attacks)*** are episodes of a progressive increase in:
  - SOB
  - Cough
  - Wheezing
  - Chest tightness
- One or a combination of these symptoms is enough.

Cont.

- Do not underestimate the severity of an attack
  - Severe asthma attacks may be life threatening
  - Treatment requires close supervision

19.25 Immediate assessment of acute severe asthma

Acute severe asthma

- PEF 33–50% predicted (< 200 L/min)
- Respiratory rate ≥ 25 breaths/min
- Heart rate ≥ 110 beats/min
- Inability to complete sentences in 1 breath

Life-threatening features

- PEF < 33% predicted (< 100 L/min)
- SpO_2 < 92% or PaO_2 < 8 kPa (60 mmHg) (especially if being treated with oxygen)
- Normal or raised $PaCO_2$
- Silent chest
- Cyanosis
- Feeble respiratory effort
- Bradycardia or arrhythmias
- Hypotension
- Exhaustion
- Confusion
- Coma

Near-fatal asthma

- Raised $PaCO_2$ and/or requiring mechanical ventilation with raised inflation pressures

Patient features suggestive of a severe attack:

- Breathless at rest
- Hunched forward
- Talks in words rather than sentences (infant stops feeding)
- Drowsy or confused

Patient features suggestive of a severe attack:

- Bradycardia
- RR > 30/min
- Wheeze is loud or absent
- PR > 120/min (infant >160/min)
- PEF is < 50% of predicted or personal best
- SpO_2 < 90%
- The patient is exhausted

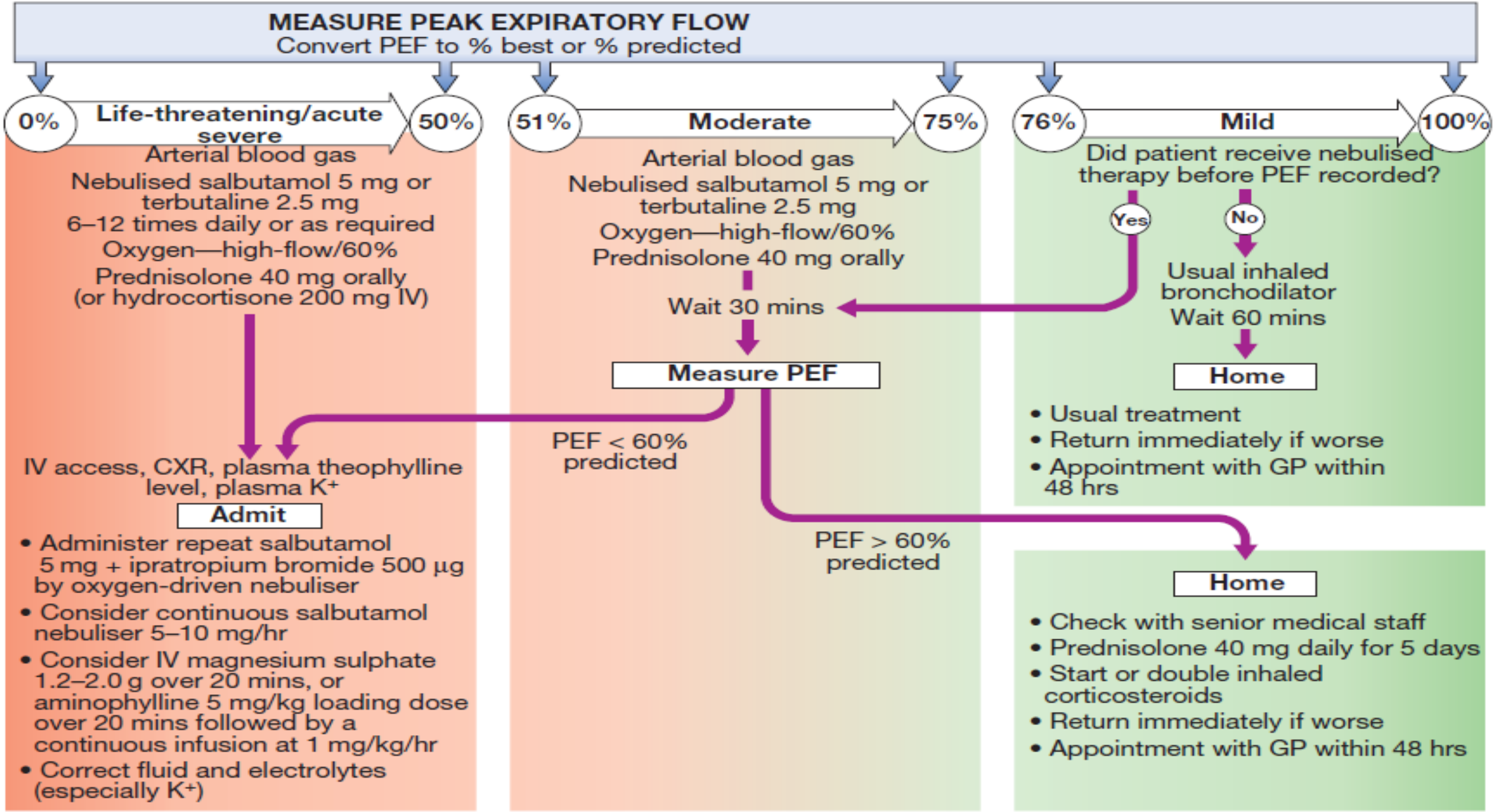


Fig. 19.24 Immediate treatment of patients with acute severe asthma.

Mild to moderate attacks management

- ***Inhaled SABA (spacer/ nebulize)***: Begin with 4 to 10 puffs every 20 minutes for the 1st hr.
- ***Oral corticosteroids***:
  - E.g. 1mg of prednisolone/kg/d introduced early in the course of a moderate or severe attack (up to 50mg for 5 – 7 days)
- If hypoxemic provide ***oxygen to achieve SPO_2 of >90%***
- Check response after 1 hr.

Severe asthma

- ***Admit***
- ***Combination SABA + ipratropium bromide nebulization***: greater improvement
- ***OCS***
- ***High flow humidified O_2 therapy***.
- ***Theophylline*** used if inhaled β – 2 agonist are not available
  - If the patient is already taking daily theophylline ***measure serum concentration before adding short acting theophylline; Narrow TI; administer slowly over 15 mins.***

Cont.

- Patients with severe asthma attacks & unresponsive to bronchodilators & systemic glucocorticoids → ***2g $MgSO_4$ IV***

Common Adverse effects

- ***SABA***: Tremor, tachycardia; Tolerance develops
- ***LABA***: Tachycardia, headache, cramps
- ***ICS***: Oropharyngeal candidiasis, dysphonia
  - Advise patient to rinse and spit.
- ***OCS***
  - Short term: hyperglycemia, GIT effects, mood changes
  - Long term: additional systemic effects
    - When taken for up to 2 weeks, OCS can be stopped abruptly. Beyond 2 weeks, the dose must be tapered off to avoid precipitating an Addisonian crisis.

Cont.

- ***LTRB***: increased LFT
- ***Anticholinergics***: dry mouth or bitter taste

References

- GINA (global initiative for asthma) pocket guide 2018
- Inhaler charts on GINA website

TYPED BY NAILA KAMADI

- *Courage* -

The greatest victory in living

Lies not in never failing,

But in rising every time we fall.

“I can do all things through Christ who strengthens me.”

- Phil. 4:13 -

4. NEURO – THERAPEUTICS NOTES LEVEL VI MBCHB 2019

COMPILED BY NAILA KAMADI

OUTLINE

Management of seizure disorders

Treatment of CNS degenerative disorders

Treatment of pain

Management of neuropsychiatric diseases

1. MANAGEMENT OF SEIZURES

8TH/2/2019

BY: DR. OCHANDA

Definition of terms

- **Seizure**: *excessive*, *uncontrolled* release of *paroxysms of electrical activity* from an area of the brain. The spread of the excessive electrical activity may be **local** or **generalized**.
- Seizures may manifest as:
  - Loss of consciousness
  - Motor activity: may be tonic, clonic, tonic clonic, atonic
  - Sensory activity: visual, auditory, gustatory, olfactory, tactile, pain
  - Psychological experiences

Cont.

- **Epilepsy**: Epilepsy is defined as ≥ 2 unprovoked seizures at least 24 hrs. apart. It is a tendency towards continuity/ recurrence of seizures.
- **Fits**: is used generally to referred to GTCs
- **Convulsions**: seizures that manifest with motor activity esp. the GTC variety.

Epidemiology

- *5 – 10%* of the general population has had a seizure during their lifetime. This proportion does not necessarily have epilepsy.
- Incidence of epilepsy is *0.3 – 0.5%* worldwide
- Prevalence of epilepsy is *5 – 10 per 1000*.

Classification according to ILAE 1981

- Partial seizures: Simple partial (motor, sensory, autonomic psychic signs); complex partial; partial seizures secondarily generalized
- Generalized seizures: accompanied with loss of consciousness.
- Unclassified seizures

*Partial seizures

- **Simple partial**: motor, sensory, autonomic, psychic signs
- **Complex – partial**: accompanied with *alteration of mental activity* e.g. sleep walking.
- **Partial seizures secondarily generalized**.

Generalized seizures include:

- Grand mal (tonic – clonic): 10% of all
- Absence (petit – mal): 15 – 20% of childhood epilepsies
- Tonic seizures
- Atonic (drop attacks) seizures
- Myoclonic seizures

Unclassified

- Neonatal seizures
- Infantile spasms

3 points to note about seizures

- There is a focal point in the brain from which this abnormal activity is induced without control.
- The activity spreads.
- Status epilepticus: repeated convulsions without recovery.

Pathophysiology

- Opening of sodium channels in association with potassium channels (channelopathies)
- Mutations alter one of the subunits of the channels resulting in alteration of the closing & opening mechanisms of the channels.
- Result is abnormal opening of the channels → seizure.

Epilepsy Syndromes

Juvenile Myoclonic Epilepsy (JME)

- Common in early adolescence (10 – 13 years).
- Myoclonus may be accompanied with tonic – clonic seizures.
- 1/3 have petit mal seizures as well.

Cont.

Lennox Gestaut Syndrome

- Occurs in children
- Characterized by *multiple seizures*:
  - Usually tonic clonic is present
  - At times clonic, atonic & atypical absence (last longer & are accompanied by motor activity)

Cont.

- EEG shows a ***slow < 3Hz spike & wave discharge***.
- These children have *impaired cognitive function* (disabilities in learning, memory, concentration)
- Associated with *CNS disease or dysfunction* e.g. past meningitis, encephalitis, perinatal HIE

Cont.

Mesial Temporal Lobe Epilepsy Syndrome (MTLE)

- Has typical clinical, EEG & pathological features
  - Pathology: hippocampal sclerosis
- The MC syndrome associated with complex partial seizures.
- Tends to be *very resistant to drugs*.
- Usually *cured by surgery*.

Cont.

West's syndrome

- Clinical triad of:
  - Infantile spasms
  - Arrest of psychomotor development
  - Hypsarrhythmia on EEG
- Causes can be prenatal, perinatal or postnatal

Cont.

- Up to 40% have no cause
- Onset is usually before 1 year; peaks at 3 – 7 months
- Prognosis is very poor if patient has infantile spasms
- Drug of 1st choice is: **vigabatrin**
- Also: valproate, clonazepam & zonisamide
- ACTH, steroids can be used when others fail.
- Focal lesions respond to surgery

Cont.

Landau – Kleffner syndrome

- Presents as an acquired aphasia with seizures
- Several seizure types occur including: GTC, partial and myoclonic seizures
- Characteristically manifest with word deafness despite normal hearing.

Cont.

- EEG shows **spike activity over temporo – central regions**
- Occurs at 3 – 9 years.
- Responds to standard drugs
- Language recovery is variable.

Etiology

- There are 2 types of epilepsy:
  - Idiopathic
  - Secondary

Neonatal causes

- Prenatal
  - Hypoxic – ischemic encephalopathy
  - Intracranial hemorrhage, trauma, acute CNS infection, metabolic disturbances (hypocalcemia, hypomagnesemia, hypoglycemia, decreased pyridoxine), drug withdrawal, developmental diseases, genetic abnormalities

Infants/ children (1 – 12 yrs.)

- Febrile seizures
- Genetic diseases
- CNS infections
- Trauma
- Developmental diseases
- Idiopathic

Adolescents (12 – 18 yrs.)

- Trauma
- Genetic diseases
- Infection
- Brain tumors
- Illicit drug use
- Idiopathic

Young adults (18 – 35 yrs.)

- Trauma
- Alcohol withdrawal
- Illicit drug use
- Brain tumors
- Idiopathic

Older adults

- CVA
- Brain tumors
- Alcohol withdrawal
- Metabolic diseases: anemia, liver failure, electrolyte abnormalities, hypoglycemia
- Alzheimer’s disease, other degenerative diseases
- Idiopathic

Drugs + other substances causing seizures

- Antibiotics: beta lactams, quinolones, INH, acyclovir, ganciclovir
- Anesthetics/ analgesics: meperidine, tramadol, LAs
- Immunomodulatory drugs: cyclosporine, tacrolimus, IFNs
- Psychotropics: antidepressants, antipsychotics, lithium
- Theophylline
- Radiocontrast agents
- Sedative/ hypnotics withdrawal: alcohol, BDZ, barbiturates
- Drugs of abuse
- Amphetamine, cocaine, phencyclidine, methylphenidate
- Flumazenil

Drug mechanisms

- Inhibition of sodium channels
  - Phenytoin
  - Carbamazepine
  - Topiramate
  - Zonisamide
  - Felbamate

Cont.

- Inhibition of voltage gated Ca^{2+} channels (good for partial seizures)
  - Phenytoin
  - Ethosuximide
  - Valproate
  - Trimethadione

Cont.

- Decrease glutamate release:
  - AMPA receptors: Lamotrigine, topiramate
  - NMDA receptors: Felbamate
- Potentiation of GABA receptor function (*they increase chloride*)
  - BDZs
  - Barbiturates
  - Topiramate
- Increase in availability of GABA
  - Valproate, gabapentin: inhibit GABA transaminase
  - Tiagabine: inhibits GABA reuptake

Chemical classification of drugs

- **Hydantoins**: phenytoin, methotoin, ethotoin, phenacemide
- **Imminostilbenes**: carbamazepine, oxcarbazepine
- **Barbiturates**: phenobarbital, primidone
- **BDZ**: diazepam, clonazepam, clorazepate, dipotassium Nitrazepam
- **Carboxylic acids (fatty acids):** valproic acid, sodium valproate
- **Succinamides**: ethosuximide, phensuximide, methsuximide
- **Oxazolidinediones**: trimethadione, dimethadione, paramethadione
- **Steroids**: ACTH, Prednisone
- **Miscellaneous:** Vigabatrin, Lamotrigine, Levetiracetam, Felbamate, Acetazolamide, Zonisamide.
- **Amino acids:** 5 – HT (***for myoclonus in resistant infants***)

Drugs & their indications

Carbamazepine (Tegretol, zheptol)

- 400 – 1600mg/d in 2 – 3 divided doses; therapeutic levels (20 – 50μmol/L)
- 1st line or adjunctive therapy in:
  - ***Partial & generalized seizures*** (except petit mal & myoclonus)
  - Lennox Gestaut Syndrome
  - Childhood epilepsy syndromes

Cont.

Clobazepam

- 10 – 30mg/d, in 1 – 2 divided doses
- Adjunctive therapy for partial and generalized seizures.
- Also for intermittent therapy, on/off prophylactic therapy, non – convulsive status epilepticus
- Excellent second line for some resistant epilepsy.

Cont.

Clonazepam (rivotril)

- initially 0.25mg, maintainance 0.5- 4mg per day in 1-2 doses, or 0.1- 0.2 mg /kg in adults, children 0.01 – 0.02 mg/kg//d.
- Therapeutic levels, 5-70ng/ml
- Adjunctive therapy in partial and generalised seizures, including absence and myoclonus, Lennox Gestaut syndrome, status epilepticus.

Cont.

Lamotrigine (lamictal)

- initially 12.5-25mg/d, maintenance 100-200mg/d.
- Monotherapy or comedication with valproate, Comedication with enzyme inducers 200 – 400mg/d
- Adjunctive or mono therapy in partial and generalized epilepsy, Lennox Gestaut syndrome.

Phenytoin (dilantin)

- initially 300mg, maintainance 100-300mg/d in adults, children 5mg/kg, maintainance 3-8mg /kg. Adjustment guided by serum levels. Therapeutic levels – 40-80μmol/l (10-20μg/ml)
- Given orally or I.V in 1-2 doses.
- First line or adjunctive therapy for partial and generalized seizures, excluding absence and myoclonus, Lennox Gestaut syndrome (LGS), childhood epilepsy syndromes.
- Use limited by adverse effects.

Cont.

Valproate (depakene, depakote, epilim)

- initially 400 - 600mg/d in adults in 2-3 divided doses, maintenance 500-2500mg/d in adults.
- 20mg/kg/d in children < 20kg, 40mg/kg/d in children >20/kg
- Therapentic levels - 300-600 μmol/l
- Drug of choice in primarily generalised epilepsy and useful in many others – myoclonus, absence, partial.

Cont.

Felbamate (felbatol)

- initially 1200mg/d in adults, in 3-4 divided doses, maintenance 1200-3600mg/d. Children - initially 15mg/kg/d, maintenance 45-80 mg/kg/d.
- Adjunctive therapy in refractory partial and secondarily generalized seizures, Lennox Gestaut syndrome, highly effective in severe resistant epilepsy but use limited by rare but severe hepatic and hematological toxicity.
- Therapeutic levels 200- 460µmol/l.

Cont.

Gabapentin (neurontin)

- 300 – 1800mg/d; Adjunctive therapy for refractory partial & secondarily generalized seizures. Well tolerated.

Levetiracetam (keppra)

- 1000 – 3000mg/d; Adjunctive therapy in partial ± secondarily generalized seizures

Oxcarbazepine (trileptal)

- Initially 600mg/d in 2 divided doses; Maintenance 900 – 2400 mg/d.
- Structure similar to carbamazepine but better tolerated with fewer adverse effect
- Adjunct or monotherapy in partial and secondarily generalized seizures.

Cont.

Primidone (mysolin)

- Initially 125mg/d in 1-2 divided doses
- Maintenance 500-1500 mg/d. Children < 2yrs – 250 - 500mg, 2-5 yrs 500-700mg, 6 - 9 yrs 750-1000mg.
- Adjunctive therapy in partial and secondarily generalised seizures, absence, myoclonus, L.G.S. Active metabolite is phenobarbital.

Tiagabine (gabatril)

- Initially 15mg/d in 2-3 divided doses Maintenance 30 – 45 mg/d (and in combination with enzyme inducers)
- 15-30 mg/d combined with nonenzyme inducers.
- Adjunct therapy for partial and secondarily generalized seizures, especially refractory cases.

Cont.

Vigabatrin

- Initially 1000mg /d in 2 divided doses, maintenance 1000- 3000mg/d, children 40mg/kg /d
- Adjunct therapy in partial and secondarily generalised seizures. Use limited by neuropsychiatric side effects and visual field constriction.

Topiramate (topamax)

- Initially 25-50 mg/d in 2 doses, Maintenance 200-600mg/d.
- Adjuct therapy in partial and secondarily generalised seizures, LGS and grand mal seizures.

Cont.

Ethosuximide (zarontin)

- Initially 250mg in 2-3 divided doses, children 10-15 mg/kg, Maintenance – 750 – 2000mg in adults, 20-40mg/kg /d in children.
- Therapeutic levels 300-700µmol/l

Piracetam

- Initially 7.2 g/d in 2-3 divided doses, maintenance upto 24g/d.
- For some patients with refractory myoclonus

Cont.

5 - Hydroxytryptophan

- For intention myoclonus

Steroids - ACTH

- 25-40 units/d, upto 240 units/d
- prednisone - 15- 60 mg/d
- prednisolone 2 mg/kg /d
- dexamethasone 0.3 mg/kg/d
- For refractory infantile spasms and myoclonus

Cont.

- **Trimethadione**
- 900-2400 mg /d in adults,
- children 30mg /kg/d
- Therapeutic level >700µg/ml
- Not used because of severe adverse effects on bone marrow, kidney and liver. It used to be the drug choice for petit mal.

Lorazepam

- - 2-3 mg b.d I.V in normal saline infusion.
- For status epilepticus.

Cont.

Clorazepate dipotassium

- 45mg/d in 2-3 divided doses,
- initially 7.5 – 22.5 mg
- For myoclonus.

Nitrazepam

- For infantile spasms and myoclonic seizures.
- Less potent than clonazepam.

Acetazolamide

- – 250 - 500mg/d. or 10/kg, max 1000mg
- Effective as adjunct therapy in catamenial epilepsy, started 7-10days prior to onset of menses and until bleeding stops.

Cont.

Phenobarbital (gardenol, luminal)

- 30 – 180 mg/d in 1 – 2 divided doses in adults; 3 – 8mg/ d in children; 3 – 4 mg/d in neonates PO.
- IM or IV 50 – 200mg repeated PRN, maximum 600mg, in status epilepticus
- Adjunct or first line therapy in ***partial or generalized seizures + absence + myoclonus, status epilepticus, Lennox Gestaut syndrome, childhood epilepsy syndromes, febrile seizures, neonatal seizures***.
- Therapeutic levels ***40 – 170 µmol/l***

PRINCIPLES OF MANAGEMENT OF EPILEPSY

- Early diagnosis & treatment of seizure disorders with a ***single appropriate agent*** offers the best prospect of achieving prolonged seizure free periods with the lowest risk of toxicity.
  - Get an accurate history from a third party. 80% of diagnosis is made on history. Merely 40% of epilepsy cases are diagnosed via EEG since most EEGs are taken inter – ictally.
  - Up to 10% of epilepsy have a treatable cause.

Cont.

- An attempt should be made to ascertain the cause, as it may be correctable. ***This is most likely in the very young & those with the first episode in adulthood***. Remember, up to 10% of epilepsy is secondary to an underlying cause.
- The goal of therapy is to keep the patient seizure free without interfering with normal function. Drug adjustments are best assisted by drug plasma levels.

Cont.

- Treatment should be initiated with a single drug. Adjust doses upwards for control until maximal doses are reached or until toxicities are intolerable. ***Large doses are started only if there is urgency in controlling the seizure***.
- Substitute a drug if maximum doses have not achieved control before using combinations.
- After seizure free period of 3yrs, you can start withdrawing the drugs. 70% children, 60% adults will have seizures controlled and can do without drugs after this period.
- Any drug should be withdrawn gradually

Simple, complex partial & secondarily GTCs

- ***Carbamazepine*** & ***phenytoin*** are the most effective single drug therapy of a partial and GTC epilepsies. The choice depends on toxicity considerations.
- Long term use of Phenytoin causes ***untoward cosmetic effects*** e.g. ***hirsutism, coarsening of facial features, gingival hypertrophy***, so it is often avoided in young patients.
- Carbamazepine can cause ***leukopenia***, ***aplastic anemia*** or ***hepatotoxicity*** & is therefore not appropriate for patients predisposed to these conditions.

Cont.

- ***Valproic acid*** is broad spectrum and is preferred for patients with ***mixed seizures*** especially the epilepsy syndromes. It is an effective alternative for partial seizures especially with secondarily generalized seizures.
- It rarely causes reversible BM suppressions & hepatotoxicity which may be fatal. Avoid in those with BM or liver disease. Risk of the fatal liver failure is higher in ***those < 2yrs. age, those on multiple drugs and those with inborn errors of metabolism***.
- It is used in infants and young children only if benefit outweighs risk. It more commonly causes ***tremors*** and ***weight gain***.

Cont.

- ***Lamotrigine, gabapentin, topiramate, Tiagabine and Phenobarbital & primidone*** are additional drugs used for partial seizures with or without secondary generalization.
- ***Lamotrigine*** is as effective as the standard drugs and is used as monotherapy. It may cause rash in children especially. It is introduced gradually from small doses when added to valproate. It inhibits its metabolism. Gabapentin has no significant drug interactions making it a useful add on therapy.

Cont.

- ***Phenobarbital*** and ***primidone*** cause sedation adults, hyperactivity in children and other subtle cognitive changes. Primidone causes more toxicity including nausea, dizziness, ataxia, somnolence & decreased libido.
- Their use should be limited to situations in which there is no suitable alternative.

Cont.

- ***Oxcarbazepine*** is as effective as carbamazepine with less adverse effects.
- Benzodiazepines are used for limited periods as tolerance to them develops.
- Clobazepam, tiagabine, vigabatrin, piracetum, felbamate, topiramate, levetiracetam are currently reserve drugs, for resistant cases.
- Felbamate rarely causes severe hepatic and hematological toxicity.

Absence seizures

- Drug of first choice for both typical & atypical absence seizures is **ethosuximide**
  - A/Es: GIT effects like nausea and vomiting. Rarely causes marrow suppression.
- Sodium valproate is equally effective; it is the second choice.
- **Clonazepam**: useful esp. in those with a myoclonic component.

Myoclonic seizures

- **Valproate** is the drug of first choice.
- **Clonazepam**: equally effective & its effect can be dramatic
- **Nitrazepam:** also effective but not available in the country.

Tonic & Atonic seizures

- Difficult to treat.
- Drug of choice:
  - Sodium valproate
  - Carbamazepine
  - Phenytoin

Febrile seizures

- Common in children.
- 2 – 3% of cases become epileptic in later years.
- Factors associated with risk of epilepsy
  - Neurologic disease
  - Developmental delay
  - Family history of epilepsy
  - Complicated febrile seizure i.e. > lasting > 15 min., one sided, several attacks in a day.
- Phenobarbital prophylaxis has been used before but current recommendations are **rectal diazepam** during the fever.

Seizures in infants and young children

- Infantile myoclonic spams with hypsarrhythmias (JME & neonatal myoclonic seizures) are refractory to the usual anti – seizure agents.
- ***ACTH*** & ***adrenal corticosteroids*** are the drugs of choice.
- Valproate & clonazepam may be effective.
- Valproate is effective for akinetic myoclonic and atonic seizures in young children.

Status epilepticus

- It is a medical emergency
- It is defined as continuous seizure attacks without resolution.
- Mortality is 3 – 35%.
- Signs become subtle after 30 – 45 minutes of continuous fits, therefore monitor with EEG.

Cont.

- Benzodiazepines are the first drugs of choice for initial treatment:
  - Diazepam (0.2mg/kg) 10 – 20 mg IV stat as a bolus
  - Then 40mg in 500ml 5% dextrose to run slowly over 6hrs
  - If it recurs you can give another bolus. At the same time start a longer acting drug like phenytoin IV (120 mg TDS) or orally
  - Lorazepam 0.1 mg/kg at 2mg/min

Cont.

- ***Phenytoin*** IV 15 – 20 mg/kg at 50mg/ min. additional doses of 5 – 10mg/kg can be given if fits continue
  - Also 1g can be given over 24 hrs.
  - 500mg stat then repeat after 12h
- ***Phenobarbital*** 20mg/kg IV at 50 – 75mg/ min. additional doses of 5 – 10mg/kg can be given if fits still continue.
- ***Sodium valproate*** can be used.
- ***Anesthetic agents*** are administered if the seizures remain refractory in ICU: thiopentone sodium, midazolam or propofol; assisted respiration if still persisting: should be in ICU with EEG monitor; acute cardio respiratory problems.

Cont.

- Administer the GA with muscle relaxants: pancuronium or atracurium then support respiration
- For G.A with assisted respiration if fits still persist.
- ahould be in I.C.U with EEG monitor. Attend to acute cardio - respiratory problems.

Treatment of refractory epilepsy

- About 1/3 patients of epilepsy are resistant to a single drug and require multiple drug therapy. The most likely are :
  - Focal epilepsy related to a structural lesion
  - Multiple seizures patients
  - Those with developmental delay
  - Tonic & atonic seizures

Cont.

- In most cases, the initial combination therapy, combine the first line drugs i.e. carbamazepine, phenytoin, valproate, lamotrigine.
- If these are unsuccessful then addition of a newer drug like topiramate, gabapentin is indicated.
- In resistant absence seizures, valproate can be added to ethosuximide. Potential drug interactions should be recognized.
- If there is no improvement with two drugs, a third can be added to the first two.
- It there is improvement, the least effective of the first two should be gradually withdrawn.

Surgery

- For those resistant to combination therapy, surgery can be extremely effective in substantially reducing seizure frequency and even may give complete seizure control.
- The most common surgical procedure for those TLE is temporal lobectomy

Other procedures are:

- Hippocampal and amygdala limited removal
- Focal neocortical resection
- Lessionectormy
- Multiple subpial transection
- Hemispherectomy
- Multilobar resection
- Corpus callostomy

Vagus nerve stimulation

- This for patients with refractory epilepsy who are not candidates for surgery
- A bipolar electrode is placed on the cervical portion of the left vagus nerve and connected to a small subcutaneous generator put in the infraclavicular region. It delivers intermittent impulses to the vagus nerve. Side effects are mild and transient.

Epilepsy in pregnancy

- Rates of still births and infant mortality are higher for epileptic mothers. Drug administration in first trimester especially increases incidence of birth defects. Combination therapy cause increased incidence of birth defects. Increase is up to 7% compared to 2-3 % in normal.
- Nevertheless most women with epilepsy will have uncomplicated gestation delivery normally. Seizure frequency remains the same in 50%, increases in 30% and decrease in 20% .

Cont.

- Phenytoin, valproate, carbamazepine cause a syndrome of ***facial dysmorphism***, cleft lip cleft palate, cardiac defects, digital hypoplasia and nail hypoplasia.
- Valproate and carbamazepine are associated with 1-2% incidence of ***neural tube defects, spina bifida***.
- Carbamazepine will in addition cause ***developmental delay***.
- A combination of carbamazepine, valproate and either phenytoin or phenobarbital causes the greatest incidence of congenital malformations.
- **Safest**: levetiracetam which can be used for both partial and generalized seizures.

To minimize drug effects

- Use a single drug at the lowest dose possible to control generalized tonic/clonic fits.
- Divide doses into 2 per day to minimize plasma drug level peaks
- Trimethadione and valproate should be avoided in pregnancy.
- Patients should take folate 1 – 4 mg OD
- Enzyme inducing drugs like phenytoin, phenobarbital, primidone cause deficiency of vit. K depended clothing factors in 50% newborns. Give vit.k 1mg at birth.
- Monitoring drugs plasma levels useful to reduce toxicity.

Contraception

- Many drugs e.g. carbamazepine, phenytoin, Phenobarbital, topiramate, can significantly antagonize effects of oral contraceptives.
  - They induce enzymes.
- Either use other methods or modify drugs dosage

Breastfeeding

- Most anticonvulsants are excreted in milk. Ratio of milk to plasma concentrations are:
- Ethosuximide 80%
- Phenobarbital 40 – 60%
- Carbamazepine 40%
- Phenytoin 15%
- Valproate 5%
- Nevertheless drugs are freely given in lactation, only changed if drug effects on infant such as lethargy, poor feeding occurs.

2. TREATMENT OF CNS DEGENERATIVE DISORDERS 6/7/2019

BY: DR. OCHANDA

DEFINITION

- A group CNS disorders in which there is gradual, generally symmetric, relentless progressive wasting away of neurons for reasons still unknown. Some are genetically dependent.

CLASSIFICATION

- 1. Syndromes in which progressive dementia is the major manifestation
- A) Diffuse cerebral atrophy
- - Alzheimer’s disease
- - Senile dementia
- - Corticobasal degeneration
- - Dementia with Lewy bodies
- - Ischemic vascular dementia

- Creutzfeld Jacob’s disease
- B) Circumscribed cerebral atrophy – frontal dementias,-Pick’s disease, fronto-temporal dementia with Parkinsonism
- 2. Syndromes in which progressive dementia is combined with other neurologic signs
- A) Principally in adults
- Huntington’s chorea

- Cerebro-cerebellar degeneration
- B) In children and adults
- Amaurotic family idiocy(neuronal lipidoses)
- Leukodystrophy
- Familial myoclonus epilepsy
- Hallervoden-Spatz disease
- Wilson’s disease(hepatolenticular degenration

- 3. Syndromes in which there is gradual development of abnormalities of posture and involuntary movements
- Parkinson’s disease
- Dystonia vasculorum deformans(Torsion dystonia)
- Familial tremor
- Spasmodic torticollis

- 4. Syndromes chiefly manifesting with slowly developing ataxias
- Cerebellar degenerations
- Spinocerebellar degenerations(Friedrick’s ataxia, Marie’s hereditary ataxia)
- 5. Syndromes with slowly developing muscular weakness and wasting
- A) Motor neuron disease

- In Adults:
- Amyotrophic lateral sclerosis
- Progressive muscular atrophy
- Progressive bulbar palsy
- Primary lateral sclerosis
- In Children or young adults:
- Infantile muscular atrophy

- Other forms of familial progressive muscular atrophy
- Hereditary spastic paraplegia
- B) With sensory changes
- i)Progressive neural muscular atrophy
- Peroneal muscular atrophy(Charcot-Marie-Tooth disease)
- Hypertrophic interstitial neuropathy(Dejerine-Sottas disease)

- Ii) Miscellanous forms of chronic progressive neuropathy
- 6. Syndromes chiefly manifesting with progressive visual loss
- Hereditary optic atrophy (Leber’s disease)
- Pigmentary degeneration of the retina(retinitis pigmintosa)

Multiple sclerosis

- **AETIOLOGY**
- Autoimmunity- mbp
- Infection-HHV-6, EBV, chlamydia pneumonia
- Median age 23.5 years
- Clinical
- Cognitive impairment
- Cranial nerve dysfunction

- Impairment of sensory pathways
- Impairment of motor pathways
- Impairment of cerebellar pathways
- Bladder bowel, sexual dysfunction
- Special features: Lhemite’s sign, Uhthoff’s sign, fatigue

Diagnostic criteria

- Definite
- Likely
- Probable
- unlikely

Treatment

- Acute - Methyl prednisolone 1g x 5 days
- RR- Interferon beta-1b avonex 30 mcg im weekly, betaseron 1ml sc od, beta 1a(rebiff) 22-44mcg sc 3x weekly
- Glatiramer acetate(copaxone 20mcg sc 3x daily
- Oral immunosuppressants-methot, cladribine
- Cyclophosphamide for difficult cases, IV monthly mitoxantrone(novantrone)

- Tremors –INH 800-1200mg/d, B6 100mg od, anticonvulsants- primidone, gabapentine, carbamazepine
- Spasticity – tizanidine, baclofen
- Fatigue- modafinil 200-400mg/d
- Depression- SSRIs
- Bladder dysfunction – amitryptylline
- Plasmapheresis

Parkinson’s disease

- Diagnosis
- Staging
- Treatment
- Basal ganglia disease characterised by: rigidity, tremors and bradykinesia
- Diagnosis clinical

- Staging: 1-4
- Drugs
- 1. L-Dopa
- 2. Dopamine agonists – bromocryptine, carbegoline, pramipexole, ropinorole, apomorphine
- 3. MAO B inhibitors – selegeline
- 4. COMT inhibitors – entacapone, tolcapone

- 5. Anti-muscurinics – Benzhexole(artane)
- 6. Amantadine
- Challenges:-
- Non-response
- End of dose phenomenone
- On-off phenomenone

ATAXIAS

- Types
- Clinical signs
- Treatment
- Characterised by gait impairment, slurred speech, visual blurring, hand incoordination and tremor with movement.
- Classified as Acute, subacute, chronic

- Acute causes
- Sub-acute causes
- Chroniv causes
- INHERITED ATAXIAS:
- May be AD, AR, X-linked
- Typical example is Friedrick’s ataxia

FREDRICK'S ATAXIA

- The most common inherited ataxia. Can occur with vitamin E deficiency syndrome. Autosomal recessive inheritance.
- S/S
- - presents at <25 yrs, progressive and staggering gait, frequent falling, titubation, lower extremities more involved. Dysathria may be the presenting symptom.

- Rarely progressive scoliosis, foot deformity, nystagmus or cardiomyopathy the presenting symptom.
- Extensor plantar responses(with normal tone), absence of reflexes, weakness greater distally are usual. Vibration, proprioception loss may occur
- Median age of death is 35 yrs, women have a better prognosis

- Cardiac involvement in 90%
- Mental retardation, psychiatric disease occur in a few
- 20% have diabetes mellitus
- Muscullo-skeletal deformities common
- MRI spinal cord shows atrophy. Primary site of pathology are spinal cord, dorsal root ganglion cells, peripheral nerves

- Slight atrophy of cerebellum and gyri may occur
- Sclerosis and degeneration seen in spino-cerebellar tracts, lateral cortico-spinal tracts, posterior columns
- Genes 9q13-q21.1 and mutant gene frataxin- expanded GAA triplets repeats

TREATMENT

- Identify treatable causes
- Mass lessions remove
- Paraneoplastic disease treat cause
- Anti-gliadin Abs and gluten sensitive enteropathy – treat with gluten free diet
- Malabsorption syndromes – vit E deficiency treat, vit B1, vit B12 deficiency treat
- Hypothyroidism treat

- Syphilis, lyme disease, legionella’s disease treat
- Avoid alcohol, phenytoin in these patients
- Dietary measures for aminoacidopathies, leukodystrophys, urea cycle abormalities, mitochondrial encephalopathies will help
- Ideberone a free radical scavenger may improve cardiomyopathy in Friedrick’s ataxia

- Riluzole has some benefits
- Acetazolamide may reduce duration of episodic ataxias
- No known treatment improves neurologic function
- Identify at-risk persons and genotype, appropriate family and genetic counseling
- May reduce incidence

DEMENTIAS

- Alzheimer’s disease
- Others- vascular dementia(multi-infarct D), fronto-temporal dementia, cortico-basal degeneration, Pick’s disease, diffuse Lewy body disease, other secondary types

- Dementia is an acquired and persistent in multiple cognitive domains, severe enough to interfere with every day function. They tend to be chronic, progressive and irreversible.
- A major disease affecting 10% of those >65 yrs, 20% of those >75 yrs, 47% of those >85 yrs. 10% have a treatable reversible cause, 70% of dementias are Alzheimer's.

PATHOLOGY

- There is diffuse deterioration of mental functions manifesting primarily in thought and memory dysfunction, and secondarily in feeling and conduct. The picture varies according to previous temperament, age of onset, localization, rate of progress and nature of cause.

DIAGNOSIS

- 1. History and physical examination
- 2.Investigations
- Imaging – MRI, CT-scan, PET, SPECT, X-ray
- Hematological – hemogram, U/Es, Ca, PO4, serum B12, folate levels, serum lipids, VDRL,ELISA for HIV, serum proteins, electrophoresis, TFTs, serum copper levels if indicated

- EEG
- CSF studies, Tau protein, beta amyloid
- Genetic testing
- Biopsy
- Most diagnosis confirmed at autopsy

3. Psychometric tests value greater than 1.5 SD below the appropriate norm

- Instruments:
- Mini mental scale
- Alzheimer’s disease assessment scale (ADAS)
- Consortium to establish a registry of Alzheimer’s disease (CERAD)
- Bayler severe impairment battery
- University of Pennsylvania disease management protocol for dementia

- Score of >4 is cognitive impairment

Treatment

- 1. Anticholinesterase inhibitors
- Donezepil (aricept) – Long acting, half life 70 hours. Dose 5-10 mg OD
- Rivastigmine(exelon) – oral 1.5, 3, 4.5, 6 mg tabs, 2mg/ml solution. Dose
- Galantamine(reminyl) oral 4, 8, 12 mg tabs, 4mg/ml solution, Dose
- Tacrine(tetrahydroaminoacridine –THA)

- 10, 20, 30, 40 mg tabs. Dose 80-160 mg/d
- 2. NMDA receptor blockers: Memantine(namenda), 5, 10 mg tabs
- 3. Supportive treatment
- -antidepressants –SSRIs, desipramine, nortryptylline
- -agitation - phenothiazines-thioridazine, haloperidol, trazodone risperidone olanzapine

- Sedation – benadryl, alzolam
- Home nursing
- Family therapy
- Vitamin E 1000 iu BD
- Immunization for Beta-amyloid protein
- Ginko biloba
- 4. Treat causes

MOTOR NEURON DISEASE

- Progressive, devastating
- Pathology- death of anterior horn cell and upper motor neuron. May start with loss of LMN or UMN, but eventually both lost.

MOTOR NEURON DISEASE

- Causes
- Primary:
- 1. Acute - Poliomyelitis, herpes zoster, coxsachie virus
- 2. Chronic – ALS, PLS, MMN, PBP, PMA
- Secondary – structural lessions
- Infections
- Intoxications/physical agents

- Immunologic diseases
- Metabolic diseases
- Hereditary disease
- DIAGNOSTIC CRITERIA
- Definite- 3 or 4 areas involved-bulbar, cervical, thoracic, lumbo-sacral motor nerves
- Probable – when 2 sites involved
- Possible – when 1 site involved+ mutation

Epidemiology

- Incidence- 1-3 per 100,000
- Prevalence 3-5 per 100,000
- Endemic foci – Western pacific, US, Europe
- Males affected more
- Factorsimplicated – pesticides/insecticides, smoking, military service
- 5-10% inherited autosomal dominant, familial ALS inherited SUD1 mutation.

Differentials

- Look for traetable causes if- restricted to upper or lower MN, involvement of neurons other than MNs, evidence of motor neuron block
- Spinal lessions- especially cervical

Treatment

- No treatment available
- Riluzole
- Vitamine E
- ASA
- NSAIDS
- On trial- ceftriaxone, pramipexole, tamoxofen
- Rehabilitation

PROGNOSIS

- Relentlessly progressive disease, death from respiratory failure
- Median survival 3-5 years

3. TREATMENT OF PAIN
17th/6/2019

BY: DR. MOHAMED EZZI

Introduction

- An unpleasant sensory and emotional experience arising from actual or potential tissue damage.
- Most illnesses cause pain.

Introduction

- Pain acts as a ***warning signal*** that whatever is causing the pain is a ***noxious stimuli*** that requires one ***to withdraw from damaging situations***.
- Pain protects the damaged body part while they heals e.g.
- Pain enables one to avoid those situations that elicit pain.

Introduction

- Pain medicine allows restoration of normal function.
- Alleviation of pain is the aim of any therapeutic approach.
- It constitutes an important branch in medicine.

Physiology of pain

- There are 2 main types:
  1. ***Nociceptive***: pain that occurs at the point of impact e.g. hitting the little toe on a table
  2. ***Neuropathic***: pain that occurs due to nerve pathology. Presents with burning sensation & associated numbness.

Acute v/s Chronic

- Acute pain:
  - Recent onset
  - Limited duration.
  - Identifiable temporal, causal relationship.

Acute v/s Chronic

- Chronic pain:
  - Persists beyond the time of healing
  - Sometimes there is no clear identifiable cause.

Acute v/s Chronic

- Acute & chronic represent a continuum since, untreated or insufficiently treated acute pain can become chronic.

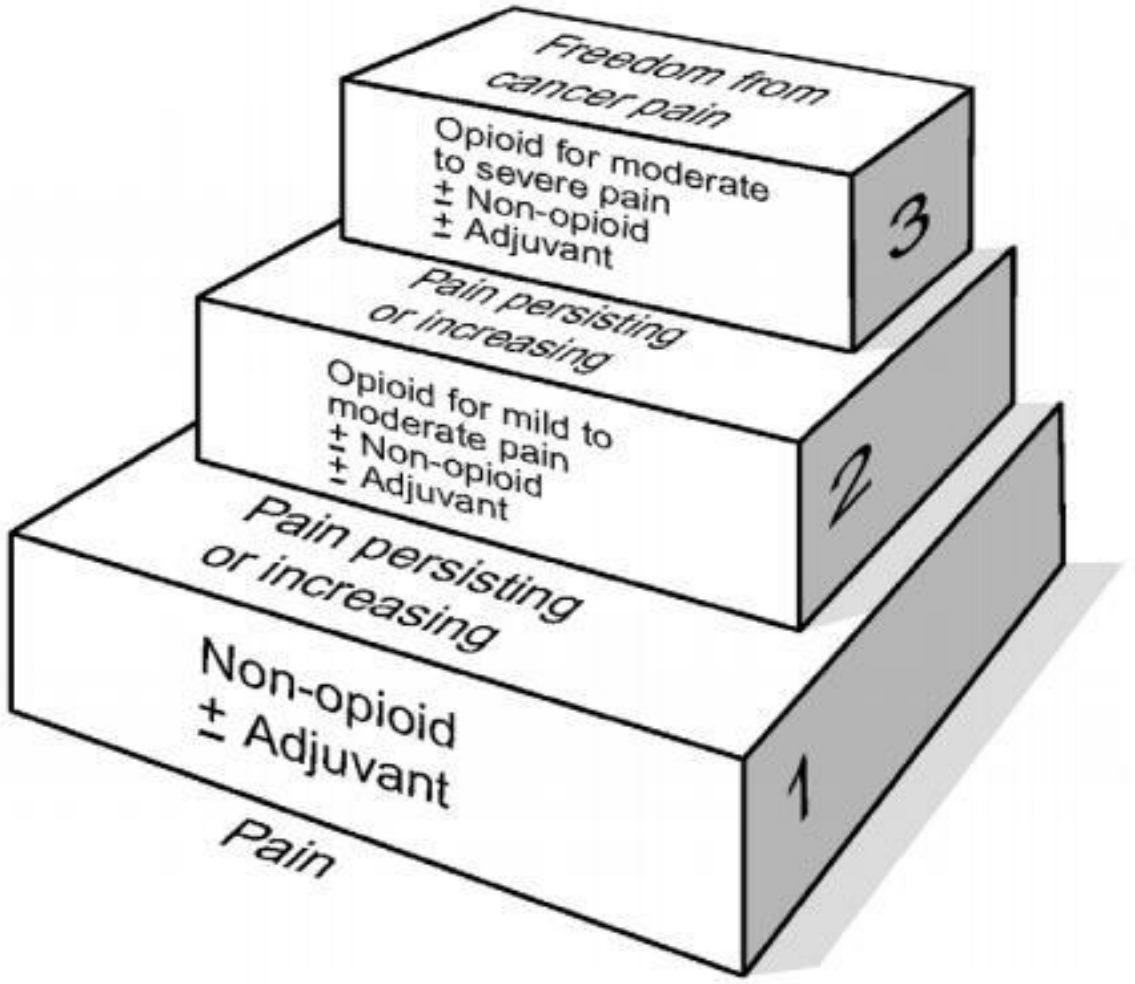
Pharmacological Management

- Management differs on whether the pain is acute or chronic.
- Mainly:
  - Opioids
  - NSAIDs
  - Acetaminophen
  - Capsaicin, inhaled NO_2 – acute
  - Antidepressant, anticonvulsant drugs: for management of chronic
  - Muscle relaxants: for management of pain associated with muscle spasm
  - Local anaesthetics: for management of neuropathic pain.

WHO Pain Ladder

- Pain is managed in a step wise approach using the WHO Pain ladder.
- Step 1: mild pain
  - Non – opioid (NSAIDs) ± Adjuvant (antidepressants, anticonvulsants)
- Step 2: mild – moderate pain
  - Opioid ± Non opioids ± Adjuvant
- Step 3: severe pain
  - Opioid for moderate to severe pain ± Non opioid ± Adjuvant

WHO Pain Ladder



Changing Analgesic/ Route of Administration

- Several analgesic options:
  - Solid oral dosage forms (tablets, capsules)
  - Oral liquids
  - Topical
  - Transdermal patches
    - Extended delivery
    - Expensive

Changing Analgesic / Route of Administration

- Considering product rotation:
  - Drug formulation, availability
  - Route of administration
  - Drug interactions
  - Adverse effects
  - Cost

Changing Analgesic / Route of Administration

- Long acting opioids:
  - Long acting morphine, hydromorphone, oxymorphone, oxycodone, methadone, fentanyl
- Multimodal therapy carries risk of additive adverse effects & drug interaction.
  - For example: Anticonvulsant + opioid = additive sedation.

Monitoring, Prevention of Side Effects

- Gabapentin: Sedation, dizziness, edema, cognitive impairment
- NSAIDs: GI upset, ulceration, easy bruising, bleeding, renal toxicity, HTN
- Opioids: constipation, dry mouth, hypogonadism (chronic), sedation, urinary retention, osteoporosis (chronic)
- TCAs: sedation, urinary retention, constipation.

Analgesics drug – drug interactions

- Antidepressants + tramadol (increase NE, 5 – HT)
  - CNS excitation (seizures)
  - Serotonin syndrome (muscle rigidity, hyperpyrexia)
  - Unpredictable, idiosyncratic reaction
- Pharmacodynamic interactions: additive sedation, dizziness, respiratory depression
- Most analgesics are substrates of CYP – 450 leading to interactions at metabolism level e.g. anticonvulsants are enzyme inducers.

Muscle Relaxant Recommendation

- Muscle relaxants is an option
  - Cyclobenzaprine
  - Tizanidine
- Work at CNS level
- Used for muscular pain, spasms associated with peripheral musculoskeletal condition.
- Chronic use of muscle relaxants is not recommended.

Benign Chronic Back Pain

- This is the MC presenting pain pathology.
- Options for management:
  - ***Acetaminophen*** is first line
  - ***NSAID*** is second – line
    - ***Trial of low dose TCAs*** if failed NSAIDs
  - If radicular pain: trial of ***gabapentin***
- Not recommended:
  - Muscle relaxants (can be used for the initial period but not chronically)
  - Opioids are not recommended for long term management

Fibromyalgia, Myofascial Pain

- Multidisciplinary approach including: physical rehabilitation, CBT, pharmacologic
- Options
  - SNRI (duloxetine, milnacipran)
  - If pain is severe: trial of tramadol
  - If with associated insomnia: Amitriptyline, pregabalin

Fibromyalgia, Myofascial Pain

- Cognitive behavioural therapy
  - Helps patient in coping with pain
  - It serves an antidepressant function.
  - It reduces health care seeking behaviour.
  - Fibromyalgia has a psychological component to it.

Post Herpetic Neuralgia Pain

- Drugs of choice:
  - First line: TCA's (amitriptyline, nortriptyline, desipramine) → it is a neuropathic pain
  - Gabapentin
  - Pregabalin
  - If severe pain: short term Opioids
  - Topical lidocaine patches
  - If associated with burning sensation: Topical capsaicin patch/cream

Modifying the Neuropathic Pain Regimen

- When starting the dose of medication, start at a lower dose & titrate upwards.
- When discontinuing, titrate downwards over a course of few weeks rather than stopping abruptly.
- This avoids:
  - Marked increase in pain
  - Withdrawal syndromes

Osteoarthritis
Acetaminophen – opioid combination

- Acetaminophen is 1st line therapy
- Maximal safe dose is 4000mg/day
- Risk of:
  - Hepatotoxicity
  - Acute nephrotoxicity
  - GIT ulcer

Osteoarthritis
Acetaminophen – Opioid Combination

- Opioid is 2nd line:
  - Start low dose, titrate upwards (less A/E)
  - Short – acting (hydromorphone, oxycodone) PRN
- Tramadol, tapentadol are alternative:
  - Mild opioid activity

Osteoarthritis
Acetaminophen – Opioid Combination

- Constipation is a problem:
  - Seen in chronic opioid therapy
  - To prevent:
    - Ensure adequate hydration
    - Use a motility – inducing laxative

Osteoarthritis
Acetaminophen – Opioid Combination

- Avoid acetaminophen – opioid combinations in chronic renal insufficiency due to the accumulation of toxic metabolites:
  - Morphine causes delirium, confusion, sedation.
  - Meperidine/ pethidine, pentazocine, propoxyphene cause seizures, cardiac arrhythmias.

Osteoarthritis
Acetaminophen – Opioid Combination

- Transdermal buprenorphine:
  - Moderate to severe pain
  - Partial μ agonist, κ antagonist
  - Less likely for respiratory depression
  - Reasonable choice for elderly

Osteoarthritis: NSAIDs

- Nonselective NSAIDs as 1st line in moderate – severe pain
  - Can be used as a second line therapy in patients who don't respond to 1st line NSAID – opioid combination.
- Toxicity most troublesome:
  - GI toxicity is common in:
    - Previous history of GI bleed
    - ≥60 years
    - Concurrent use of corticosteroids, anticoagulants
  - Nephrotoxicity is common in:
    - Pre – existing renal disease
    - Advanced age.

Osteoarthritis: NSAIDs

- COX – 2 selective are 2nd line. They have less GI toxicity but more cardiovascular risk. HTN is a predisposing factor for CVS toxicity.
  - Inhibit PGE_2: reduction in sodium excretion
  - Inhibit PGI_2: increase in vascular resistance
- Use COX – 2 selective inhibitors with caution in:
  - Renin – angiotensin blockers, diuretics
  - DM, CKD, heart failure

Osteoarthritis: NSAIDs

- Most cardiotoxic: Rofecoxib, diclofenac, indomethacin, meloxicam.
- Least cardiotoxic: celecoxib, ibuprofen, naproxen, piroxicam

Osteoarthritis: Topical Medications

- Avoids adverse renal, GIT effects.
- Topical salicylates are 1st line:
  - Rubefacient (increases blood flow) → increases delivery of nutrients (promotes healing) & wash out of toxic waste.
- Diclofenac, capsaicin are 2nd line

Cancer Pain

- Guided by WHO analgesic ladder (***stepwise approach***):
- Start with ***acetaminophen, NSAIDs, anticonvulsants, antidepressants***
- Moderate pain: add ***weak opioid***
- Severe pain: add ***strong opioid*** (morphine, hydromorphone, fentanyl, oxycodone)

Cancer Pain

- If on chronic pain treatment use opioid therapy via a Patient centred approach:
  - IV Hydromorphone (no active metabolites)
  - Transdermal fentanyl patch (continuous release)
  - Extended release morphine capsule
- If patient has chronic pain use a regular pain management rather than an ‘as & when required’ plan.

Cancer Pain

- Respiratory depression more likely in:
  - Opioid naive
  - Postoperative pain
  - PRN opioid
- Incomplete cross tolerance:
  - Diminished tolerance when changing to a new opioid
  - Requires dose reduction of the new opioid

Breakthrough Pain

- Patient on regular pain control gets severe episodes of pain exacerbation in between the doses.
- Causes: may be idiopathic, induced by a stimulus or may be due to end of dose failure (MCC).
- Classification:
  1. Spontaneous pain: no stimulus
  2. Incident pain: uncontrollable stimulus
  3. End of dose failure: end of dosing interval
- Management of break through pain: Administer a short acting opioid (***morphine, oxycodone, hydromorphone***)
- Watch out for opioid abuse. ***However, never withhold narcotic opioids in cancer patients.***

Methadone

- Long acting opioid agonist acting on ***mu, delta receptors***
- Good for ***neuropathic pain***:
  - 5-HT, NE reuptake inhibition
  - NMDA antagonist
- Also indicated in weaning off a patient who abuses opioids.
- Rotate to methadone:
  - Inadequate response to other opioids
  - Intolerable side effects
- Long half life (15 – 60 hours)

Methadone Toxicity

- Fatal respiratory depression
- QT_c interval prolongation (torsades de pointes)
  - ≥100 mg/day
  - Hypokalaemia
  - Reduced liver function
  - Cytochrome P450 drug interaction
- Discontinuing methadone

Opioid Side Effects

- Tolerance to most develops in 7 days
- If side effects don't diminish:
  - Switch to a different opioid
  - Add another medication to counteract the effect
- Respiratory depression:
  - Serious
  - Preceded by sedation
  - Reversed by ***naloxone*** (opioid receptor antagonist)

Refractory Cancer Pain

- Neuraxial opioid administration (epidural, intrathecal)
  - Indications
    - Neuropathic pain
    - Mixed neuropathic nociceptive pain
    - Radicular pain
    - Complex regional pain syndrome/ algodystrophy

Refractory Cancer Pain

- Neuraxial opioid administration (epidural, intrathecal)
  - Drugs (administered by pain specialists)
    - Opioids (morphine, hydromorphone, fentanyl)
    - local anaesthetics (bupivacaine, ropivacaine)
    - Clonidine
    - Ziconotide
    - Baclofen

Refractory Cancer Pain

- Complementary & alternative medicine:
  - Auricular acupuncture
  - Therapeutic touch / massage
  - Hypnosis
  - Music therapy
  - Meditation: yoga
- ? Medical marijuana

4. MANAGEMENT OF NEUROPSYCHIATRIC DISEASES

BY: DR. OCHANDA

5. ENDOCRINE THERAPEUTICS NOTES LEVEL VI MBCHB 2019

COMPILED BY NAILA KAMADI

OUTLINE

- Oral Hypoglycemic Agents
- Use of insulin in DM
- Management of comas in DM
- Management of complications of DM
- Management of hypothyroidism
- Management of hyperthyroidism
- Hormone Replacement Therapy
- Use of Prostaglandins in medical practice

1. ORAL HYPOGLYCEMIC AGENTS (OHA)

8TH/3/2019

BY: DR. GICHUHI

TYPED BY NAILA KAMADI

Goals of therapy

- To eliminate ***symptoms related to hyperglycemia***.
- To reduce or eliminate long term ***microvascular*** and ***macrovascular complications***.
- To have the patient ***lead a normal life***.

Glycemic control

- HbA1c → ***< 7.0%***
- Pre – prandial capillary plasma glucose → ***3.9 – 7.2 mmol/L***
- Peak 2h postprandial capillary plasma glucose → ***< 10.0mmol/L***

The glycemic goal

- The HbA1c as close to normal as possible ***without significant hypoglycemia***.
- The target of ***HbA1c should be < 7.0%.***
- A higher HbA1c target for the very young or old or comorbid conditions.
- Depends on the frequency & severity of hypoglycemia.
- HbA1c of ≤ 6% is not recommended.

Oral Hypoglycemic Agents (OHAs)

- Should not be used for glucose management of severely ill patients as insulin is preferred.
- Are ineffective in type I DM except for the ***α – glucosidase inhibitors.***

Mild to moderate hyperglycemia

- FPG of <11.1 – 13.9 mmol/L
- Single OHA
- Usually ***metformin*** or ***sulfonylurea*** (have been used for many years)

Severe Hyperglycemia

- FPG > 13.9mmol/L
- Stepwise approach used.
- Start with a single agent then add a second agent to achieve the glycemic target.
- ***Insulin can be used as an initial therapy in individuals with high blood sugars as it results in more rapid glycemic control.***

General facts about OHA

- All except the ***α – glucosidase inhibitors*** & ***Dipeptidyl Peptidase (DPP) IV inhibitors***
  - Improve glycemic control to a similar degree
  - Have no clinical advantages to one class of drugs
- ***Insulin secretagogues*** & ***α – glucosidase inhibitors*** begin to lower the plasma glucose immediately
- ***Biguanides*** & ***thiazolidinediones*** effects are delayed by several weeks to months.

Cont.

- Not all agents are effective in all individuals with type II DM (primary failure).
- Insulin secretagogues cause hypoglycemia
  - Other agents don’t directly cause hypoglycemia
- Most individuals will eventually require treatment with more than one class of OHAs or insulin
  - This reflects the progressive nature of type II DM.

Cont.

- Because mechanisms of action of the 1st & 2nd agents are different the effect on glycemic control is usually additive.
- If adequate control is not achieved with the combination of 2 agents add:
  - A 3rd agent
  - Insulin

Include:

- ***Insulin secretagogues***: Sulfonylureas (1st & 2nd generation) Non – sulfonylureas (Meglitinides, D – phenylalanine derivatives)
- ***Biguanides***: metformin
- ***Thiazolidinediones***: Pioglitazone, rosiglitazone
- ***α- glucosidase inhibitors***: acarbose, miglitol
- ***Dipeptidyl Peptidase (DPP) – IV inhibitors***: Sitagliptin, Linagliptin, Saxagliptin, Vildagliptin

Cont.

- ***Sodium glucose co – transporter II inhibitors***: Empagliflozin, Dapagliflozin, Canagliflozin
- ***Bile acid Sequestrants***: colesevelam hydrochloride
- ***Amylin analogue***: Pramlintide
- ***Glucagon Like Peptide – I receptor agonists***: Exenatide, Liraglutide

1. INSULIN SECRETAGOGUES: Sulfonylureas

1st generation

- Tolbutamide
- Tolazamide
- Chlorpropamide

2nd generation

- Glyburide/ Glibenclamide
- Glipizide
- Glimepiride
- Gliclazide

Cont.

- 2nd generation agents are preferred because they have less
  - Adverse effects e.g. hypoglycemia
  - Drug interactions
  - Frequent administration
- MoA: stimulate insulin release from pancreatic β – cells by closing the ATP dependent K^+ channel → depolarization of membrane → insulin release.
- PKs: half life of **chlorpropamide** is 24 – 48hrs (allows for OD dosing); not advisable in elderly patients; **Glipizide** has the shortest half life of 2 – 4 hrs.; **Glimepiride** is very potent with a long DoA and is approved for OD dosing.
- Start with low doses & increase every 1 – 2 weeks based on self monitoring blood glucose (SMBG).

A/E

- **Hypoglycemia**
  - Likely in elderly patients & when using drugs with longer half life
  - Associated with
    - Delayed meals
    - Increased physical activity
    - Alcohol intake
    - Renal failure: delayed insulin clearance.
  - Rx: ***IV glucose infusion for 24 – 48 hrs.*** (if using chlorpropamide)
- **Weight gain**: due to increased insulin levels & improved glycemic control.

Contraindications

- Type I DM
- Pregnancy
- Lactation
- Significant liver & renal dysfunction
- Elderly patients (*chlorpropamide is not prescribed*)

Non – sulfonylureas: Repaglinide & Nateglinide

- Include:
  1. Meglitinides: ***Repaglinide, Mitiglinide***
  2. D – phenylalanine derivative: ***Nateglinide***
- MoA: as sulfonylureas
- Rapid onset of action
- Short duration of action therefore multiple pre-prandial use
- Can be used in patients with sulfur allergy as they contain no sulfur.

2. BIGUANIDES: Metformin

- MoA: ↑ activity of ***AMP dependent protein kinase (AMPK)*** resulting in ↓ **blood glucose** via the following mechanisms:
  - ↓ hepatic glucose production & intestinal absorption of glucose
  - ↑ glycogen storage in skeletal muscle
  - ↑ insulin sensitivity

Cont.

- Does not cause hypoglycemia, i.e., it is a ***euglycemic agent*** since it does not release insulin from the pancreas.
- Promotes some weight loss.

A/E

- 20% of patients will complain of ***anorexia, nausea, diarrhea, abdominal discomfort & a metallic taste***
  - Minimize by
    - Increasing drug doses slowly (adjust after 2 – 3 weeks using SMBG)
    - Taking the drugs with meals
  - Reassure the patient that the effects are transient & dose dependent.

Cont.

- ***Reduced vitamin B12 absorption***: annual screening for deficiency
- ***Lactic acidosis*** (in high doses) due to impaired hepatic metabolism of lactic acid

Contraindications

- Renal impairment
- Hepatic disease
- Past history of lactic acidosis
- CCF
- Chronic hypoxic lung disease
- Alcoholism

Cont.

- Discontinue temporarily & if necessary use insulin:
  - Prior to IV contrast media
  - Severe illnesses
- Since all these conditions increase the risk of lactic acidosis

3. THIAZOLIDINEDIONES: Rosiglitazone, Pioglitazone

- Euglycemic agents
- Maximum clinical effects after 6 – 12 weeks of drug administration (***act through gene regulation***)

MoA

- Activate insulin responsive genes that regulate CHO & lipid metabolism.
- Increase insulin sensitivity in tissues
  - Insulin must be present for these drugs to act
- Increase glucose transport into muscle & lipid tissues by ***increasing the synthesis of glucose transporters***.

A/Es

- Anemia
- Weight gain (2 – 3 kgs.)
- Edema
  - Reduce renal sodium excretion
  - Increased vascular permeability

Cont.

- Plasma volume expansion (Discontinue if CCF develops)
- Hepatotoxicity
  - Monitor liver function every 2 months for the 1st year & then periodically
- Provide additional methods of contraception as they enhance the clearance of OCs.
- Macular edema (rosiglitazone)

Contraindications

- Hepatic disease
  - If liver enzymes are elevated >2.5X of the upper limit of the normal
  - Previous LFT abnormality while on thiazolidinediones
  - Severe CCF
  - Pregnancy

4. α GLUCOSIDASE INHIBITORS

- MoA
  - Inhibit α glucosidase in the intestine & slows absorption of carbohydrates.
  - These enzymes convert starch & disaccharides to monosaccharides.
- Do not stimulate insulin release therefore do not cause hypoglycemia (euglycemic agents).
- Reduce postprandial glucose.

Cont.

- Used at the start of a meal
  - Initially low dose at evening meal
  - Gradually increase dose over weeks – months and administer with all meals
- Don’t use together with bile acid resins and antacids.
- ***If hypoglycemia occurs while on these drugs give oral glucose and not sucrose.***

Adverse effects

- Due to undigested CHO in the colon that is fermented & releases gas
- Results in
  - Malabsorption
  - Flatulence
  - Diarrhea
  - Abdominal bloating

Contraindications

- IBD
- Gastroparesis
- Renal and liver impairment

5. DIPEPTIDYL PEPTIDASE (DPP) IV INHIBITORS

- Oral
- Include: Sitagliptin, Saxagliptin, Vildagliptin, Linagliptin
- Inhibits DPP IV (this enzymes degrades GLP)
  - Potentiate glucose mediated insulin secretion
- Reduce dose in renal dysfunction
- Do not cause hypoglycemia
- Facilitates weight loss (indicated in obese type II diabetics)

6. SODIUM GLUCOSE CO – TRANSPORTER 2 (SGLT 2) INHIBITORS

- Include: ***Canagliflozin, Dapagliflozin, Empagliflozin***
- Physiologically, glucose is filtered by the glomeruli & reabsorbed in the proximal tubules by SGLTs.
- SGLT2 accounts for 90% of glucose reabsorption
- Inhibition of SGLT2 causes glycosuria and lowers glucose levels

Cont.

- Can be used alone or in combination with other OHAs or insulin
- Cause a modest weight loss of 2 – 5 kgs.
- Efficacy is reduce in CKD
  - Not used in severe renal disease

A/Es

- Genital infections & UTIs
- Osmotic diuresis
  - Hypotension
  - Polyuria
  - Thirst
- Increased LDL cholesterol
- Dapagliflozin: ? Breast, bladder cancer

7. BILE ACID SEQUESTRANTS

- Include: Colesevelam
- Binds bile acids
- Mechanism of glucose lowering is not known

3. GENERAL PRINCIPLES OF USE OF INSULIN IN DIABETES MELLITUS 23/4/2019

BY: DR. MOHAMMED EZZI

TYPED BY NAILA KAMADI

Which patients need insulin

- All patients with type 1 DM (*due to autoimmune destruction of pancreatic β cells*).
- 2^0 DM (*due to pancreatic insufficiency e.g. due to chronic alcoholism, chronic pancreatitis*)
- Type 2 DM (*a disease of insulin resistance in adipose & muscle tissue*) with persistent hyperglycemia on OHAs.
- Hyperglycemia emergencies: DKA or HHS

Cont.

- The following clinical features in a patient with DM (hyperglycemia) at any age:
  - Marked unexplained recent weight loss
  - Short history with severe symptoms
  - Presence of moderate to heavy ketonuria on urinalysis.

Insulin preparations available

- Biosynthetic human insulin: ***NPH*** (*Neutral Protamine Hagedorn*), ***Regular***
- Synthetic insulin analogue: ***glargine, lispro***
- Animal – sourced insulins: bovine, porcine insulins (*these are highly immunogenic*)

Human vs. analogs

- ***Human insulin preparations:*** Time to peak & DoA do not replicate endogenous insulin production.
- ***Very rapid – acting insulin analogs*** *(Lispro, Aspart, Glulisine)**:***
  - They have a faster onset of action & a shorter DoA than regular insulin.
  - They are given before a meal (pre – prandial) & hence they mimic the post – prandial endogenous insulin surge.

Cont.

- ***Short acting*** *(regular Novolin R, regular Humulin R)*
  - They are the only insulin administered IV; onset of action in 30 minutes; action peaks at 2 – 3 hrs. & duration of action is 5 – 8h.
  - Injected 30 – 45 minutes before meals.
- ***Intermediate acting*** *(NPH Humulin N, NPH Novolin N)*
  - Onset of action is 2 – 5 h. Duration of action 4 – 12 hrs.
  - Proteolytic enzyme must degrade protamine for insulin to be absorbed.
  - Administered 2 – 4 times/ day.

Cont.

- ***Long – acting analogs*** *(insulin glargine, detemir & degludec)*
  - **Detemir**: onset of action 12h; duration of action > 24h. Administered BD
  - **Glargine**: ‘peak less’; onset of action 1 – 1.5 h; maximum effect in 4 – 6 h; DoA is 11 – 24 h.; administered OD.
  - They have a longer & flatter profile than NPH hence they provide the basal insulin.

Rapid acting insulins: *Lispro, Aspart, Glulisine*

- Faster onset of action: 5 – 15 min.
  - Administered just before a meal
  - *Note: Rapid acting insulins form very little hexamers. They mostly exist in monomer form hence are rapidly absorbed & have a faster onset of action.*
- Peak action within 45 – 75 min
- Shorter DoA: 2 – 4 h
  - *Hence tends to cause less hypoglycemia*

Long – acting insulin

- ***Neutral protamine lispro:***
  - Protamine – based suspension of the rapid acting lispro.
  - It has a similar activity to NPH
- ***Insulin glargine:***
  - When given SC it will precipitate into the tissue & form hexamers hence a longer DoA of ~24hrs.
  - It is administered OD & provides the basal insulin.
  - It cannot be mixed with rapid – acting insulins in the same syringe as the insulin glargine will prevent absorption of the latter.

Cont.

- ***Insulin detemir***
  - Acylated insulin that is less potent than Glargine
  - Administered BD
  - Cannot be mixed with rapid – acting insulins
- ***Insulin degludec***
  - Longer DoA *(>40 h)*
  - Can be mixed with rapid – acting insulin

Basal vs. Bolus

- ***Basal insulin*** suppresses the hepatic glucose production hence maintaining near normoglycemia in the fasting state.
- ***Prandial/ pre – meal bolus*** covers the extra requirements of insulin required after food is absorbed.

Basal insulin

- Provided by ***intermediate long acting preparations*** which are administered OD or BD.
- Can also be achieved by a ***continuous insulin infusion*** of a short rapid – acting insulin via an insulin pump placed SC.

Bolus insulin

- Administered using a ***short acting or rapid acting insulin***.
- Provided as a ***pre – meal bolus***.

Table of insulins

Insulin therapy

- Can be divided into:
  1. Conventional therapy
  2. Intensive therapy

Conventional insulin therapy

- Simpler insulin regimen consisting of ***a single or twice daily injections of regular & NPH insulin***.
- The regular & NPH insulin are mixed together i.e. ***Mixtard formulations***.
- Fixed amounts are administered before breakfast (*am dose*) & before dinner (*pm dose*)
  - For mixtard insulin, usually 2/3 of the total dose is given in the am & 1/3 in the pm.
- Sometimes this therapy is unlikely to achieve the target HbA1c levels.

Intensive insulin therapy (basal/ bolus)

- More complex regimen that consists of a ***separate basal insulin delivery with superimposed doses of insulin boluses***.
- It requires intensive sugar monitoring before & after each meal for insulin dose titration.
- ***Note: In children, it is better for the insulin to be administered after the meal since the child may refuse to eat after receiving a pre – meal insulin bolus resulting in hypoglycemia***.

Determinants of insulin efficacy

- Type of insulin
- Site of SC depot
- Injection technique
- Angle/ depth of penetration
- Site of injection
- Alterations of SC blood flow at injection site

Cont.

Type of insulin

- Variability in the absorption & hence onset & duration of action of insulin depends on ***hexamer & monomer formation***.
- The more the hexamers the less the rate of absorption & the longer the duration of action. Monomers are absorbed faster and have a faster onset of action but shorter DoA.

Size of SC depot

- Variability in absorption is increased & net absorption is reduced with increasing the size of SC depot.

Cont.

Injection technique

- Variability in absorption is the same with insulin syringes & pen injectors.

Angle/ depth of penetration

- Very shallow insertion can cause a painful intradermal injection that is not well absorbed.
- Perpendicular injection in a lean area may result in an IM injection → more rapidly absorbed.

Cont.

Sites of injection

- Include: upper arms (triceps), abdominal wall, upper legs, buttocks
- Absorption is fastest from the ***abdominal wall*** (due to lean SC tissue) & is slowest from the ***legs & buttocks***.
- A pre – meal bolus is administered via the abdominal wall whereas the night (pm) dose is administered via the upper legs to ensure a duration of action that lasts throughout the night.
- ***When administering injections, it is advisable to rotate the injection sites to avoid lipo – hypertrophy which causes variability in absorption rates.***

Cont.

Alterations in SC blood flow at injection site

- Insulin absorption is reduced by smoking which causes thickening of capillary walls by atherosclerosis.
- SC blood flow is increased by any increase in skin temperature e.g. in exercise, saunas or hot baths, local massage.
- Absorption is more marked with regular & rapid acting insulins.

Disadvantages of using insulin include:

1. Hypoglycemia
2. Weight gain
3. Lipodystrophy
4. Hypokalemia
5. Hypersensitivity reactions

Cont.

- Hypoglycemia (*most important*)
  - The following are associated with less hypoglycemia:
    - Type II DM
    - Basal insulin
  - Type I DM & bolus insulin administration are associated with more hypoglycemia events.

Cont.

- Weight gain (*insulin is anabolic*)
  - Results in non – compliance
  - Average weight gain after 10yrs. of therapy was 7kg
  - Greater with prandial/ bolus than basal insulin

Cont.

- Hypokalemia
  - Insulin enhances intracellular shift of potassium
  - *Insulin & dextrose is a management modality of hyperkalemia*
- Lipodystrophy (*mostly lipo – hypertrophy*): occurs if injection sites are not rotated; results in absorption variability.

Cont.

- Hypersensitivity reactions
  - Common with ***porcine*** & ***bovine*** preparations
  - Less with synthetic insulins
  - Insulin inhibitors (antibodies) may be produced resulting in using very high doses of insulin to counter act their action.

3. MANAGEMENT OF COMAS IN DM 26/2/2019

BY: DR. OCHANDA

Definition

- Diabetes is a state of *sustained high blood sugars* leading to various complications due to *deficiency of insulin or resistance to it.*

Classification

- **Type I DM**: severe or absolute lack of insulin normally in those < 30 yrs.
- **Type II DM:** relative deficiency of insulin with resistance to its action, Normally in adults.
  - Maturity Onset Diabetes of the Young (MODY): _____
- **Type III DM (2^0):** caused by :
  - Multiple non – pancreatic diseases esp. hormonally ones (acromegaly, Cushing's disease)
  - Administered drugs – steroids, diazoxide.
  - Potent diabetics are those with first degree relatives with diabetes
- **Type IV: GDM**
  - Seen in about 4% of all pregnancies. Resolves after delivery.

Etiology

- Type I is autoimmune or idiopathic.
- Genetic defects in beta cell function e.g. glucokinase (MODY 2), mitochondrial DNA mutations
- Diseases of the pancreas: pancreatitis, pancreatectomy, neoplasm, cystic fibrosis, hemochromatosis

Cont.

- Endocrinopathies (hormonal): acromegaly, Cushing's, glucagonoma, phaechromocytoma, aldosteronoma, hyperthyroidism, somatostatinoma
- Drugs or chemical induced: glucocorticoids, thyroid hormones, thiazides, diazoxide, phenytoin, beta agonists, beta blockers, protease inhibitors (HAART)
- Infections (type I): congenital rubella, CMV, coxsachie virus

Cont.

- Other syndromes associated with DM: down’s syndrome, Klinefelters’ syndrome, turner’s syndrome, Friedreich’s ataxia, Huntington’s chorea, myotonic dystrophy, porphyria
- Gestational diabetes

Epidemiology

- Prevalence has risen dramatically in the past 2 decades.
- In 2000 prevalence 0.19% in < 20yrs, 8.6% in > 20yrs. And 20.1% in those > 65 yrs. M:F ratios basically the same, though slightly higher in men
- ***Scandinavia*** has the highest rates at 35/100000 per year, in type I DM, the Asiatics have the lowest, China, Japan 1 – 3/100,000 per yr. and Northern Europe and USA have intermediate rates.

Cont.

- Type II DM is highest in Pacific islands, intermediate in India and USA & lowest in Russia and China
- Incidence variation is due to genetic, environmental & behavioral factors.

Risk factors of type II DM

- Family history of DM in 1st degree relative
- Obesity, BMI > 25
- Sedentary life
- Race/ ethnicity
- Previously identified IGT (tolerance) OR IFG (fasting)
- History of GDM or baby over 4kg
- Hypertension
- High TG levels or low HDL cholesterol levels
- PCOS
- History of vascular disease

Clinical presentation

- Typically ***polyuria, polydipsia, polyphagia***
- Weight loss
- Repeated infections/ wounds
- Dehydration
- Weakness/ dizziness/ poor vision
- Acidotic breathing & coma

Complications

- DKA
- Non – ketotic hyperosmolar coma
- Hypoglycemic coma
- Repeated infections
- Diabetic foot
- Retinopathy
- Renal disease
- HTN

Cont.

- Ischemic strokes
- MI
- Diabetic diarrhea/ gastroparesis, dysmotility
- Neuropathy: peripheral, autonomic
- Cystopathy/ erectile dysfunction/ female sexual dysfunction/ retrograde ejaculation
- Dermatological disorders

Treatment

- Diet
- Lifestyle change
- Exercise
- Education on body care, hygiene, disease
- Insulin/ oral disease
- Follow up

Prevention: NEWSTART lifestyle

- ***N***utrition
- ***E***xercise
- ***W***ater
- ***S***unlight
- ***T***emperance
- ***A***ir
- ***R***est
- ***T***rust

DIABETIC COMAS

- Causes
  1. Diabetic ketoacidosis
  2. Non – ketotic hyperosmolar hyperglycemic coma
  3. Hypoglycemia

1. Diabetic Ketoacidosis

- This is a ***medical emergency***

Signs & symptoms

- Excessively high sugars > 22.4 mmol/L
- Polyuria & polydipsia
- Kussmaul's respiration
- Severe dehydration
- Comatose
- **Urinalysis**: ketonuria
- **ABGs**: ***Severe metabolic acidosis***

Cont.

- May have a history of: nausea, vomiting & abdominal pain
- P/E
  - Tachycardia
  - Severe dehydration
  - Hypotension
  - Tachypnea with acidotic breathing
  - Lethargy
  - Obtundation
  - Altered mental state
  - May be in coma or may be just comatose

Diagnosis

- History of diabetes usually (***in some instances DKA is the first presentation in a newly diagnosed diabetic patient***)
  - Presentation may be atypical
- The typical presentation history as above.
- P/E: typical features as above
- Blood sugars are elevated
- Urinalysis: ketones
- ABGs: severe metabolic acidosis
- On investigation a precipitating cause is found.

Precipitating factors

- Lack of insulin: poor compliance
- Infection
- Infarction: cerebral, coronary, mesenteric, peripheral
- Drugs: cocaine
- Pregnancy

Lab findings

- Plasma glucose: 13.9 – 33.9 mmol/l
- Na: 125 – 135 mEq/L
- K+: Normal to increased
- PO^{3-}_4: decreased
- Creatinine: slightly increased
- Osmolality: 300 – 320 mOsm/ml
- Plasma ketones: ++++

Cont.

- Serum bicarbonate: <1.5 mEq/L (***Normal: 22 – 26mEq/L***)
- Arterial pH: 6.8 – 7.3 (***Normal: 7.35 – 7.45***)
- Arterial PCO_2: 20 – 30 mmHg (***Normal: 35 – 45 mmHg***)
- Anionic gap: increased

Management

- Confirm diagnosis: hyperglycemia, ↑ serum ketones, metabolic acidosis
- Admit in ICU, especially if pH < 7 or in coma
- Assess serum electrolytes, acid base status, renal function, fluid deficit status (***usually 6 – 8 liters***)
- Insert **NGT** if vomiting or altered mental state
- Begin fluids replacement immediately aiming at about ***2 – 3 L over 1 – 3 hrs.***

Treatment: Alberti's regimen

1. Soluble insulin

- 10 units IV stat.
- 10 units IM stat
- Then:
  - Adults: 6 – 8 units/kg/ hr. on average as a continuous IV infusion
  - Children: 0.1 units/kg/hr. IV infusion
- Check Blood sugars hourly.
- Good response: the sugars should be falling by 5mmol/hr. If this is not seen in 2 – 4hrs., double or triple the dose with a maximum of a 10 fold increase.

Cont.

- Once the sugar level is down to 10mmol/L & the acidosis has resolved.
  - Adults: Give 0.05 – 0.1 units/kg/hr. until the patient wakes up & is able to take orally.
  - Children: Give 0.02 units/kg/hr.

Cont.

- When finally the patient is settled & is taking orally, calculate the **total dose [*d*] used to control sugars over the 1st 24hrs**.
- Take $\frac{2}{3}$ of that calculated total dose [*d*] & administer that amount ($\frac{2}{3}d$) of **mixtard/ lente insulin** 24 hrly as follows:
  - $\frac{2}{3}$ of $\frac{2}{3}d$ in the morning (am dose)
  - $\frac{1}{3}$ of $\frac{2}{3}d$ in the evening (pm dose)

Cont.

- Monitor the patient's sugars daily & adjust upwards or downwards to attain glycemic control. The goal of therapy is a FBS < 8mmol/L.
- At discharge, **reduce the dose by 10%** to cater for the expected reduction in insulin requirements with increased physical activity when the patient goes home.

Cont.

2. Rehydration

- The usual fluid deficit is ***6 – 8L***.
- Rehydrate using Normal Saline (NS).
- Adults: Replace at least half of the deficit in the 1st 4 hrs. the rest is replaced in the next 24 – 36hrs.
  - Children: replace at least half of the deficit in the 1st 12 hrs. the rest is replaced in the next 24 – 36hrs

Cont.

- Administer: 1L in the 1st 0.5h; then 1L in the next 1 h; then 1L in the next 2h.
- Administer maintenance IVFs using half NS (0.45%) at 150 – 300mls/kg/h.
- When sugars are <14mmol/L alternate 0.45% saline with 5% dextrose at 100 – 200 mls/h.

Cont.

Potassium Chloride (KCl)

- Always assume a K^+ deficit even if levels are normal or slightly high.
- Give 10 mEq/h KCl if:
  - Plasma K^+ is < 5.5.mEq/L, ECG is normal, urine flow has been established & normal creatinine is documented

Cont.

- Give 40 – 80 mEq/h KCl if plasma K^+ is < 3.5 mEq/L or if pH was so low that bicarbonate had to be used.
- If initial serum K^+ is < 3.3 mEq/L, do not give insulin until the K^+ level is corrected to > 3.3 mEq/L since insulin causes an intracellular shift of K^+ in exchange of H^+ ions.

Cont.

Bicarbonate (HCO_3^-)

- At a pH of > 7.2, the pH normally corrects itself when there is adequate hydration with saline.
- If the pH is 7.1 – 7.2 give 40mEq/m^2 of HCO_3^-
  - Normal BSA of a 70kg man is about 1.8m^2
- If pH is <7.1 give 80mEq/m^2 of HCO_3^-
- HCO_3^- is infused over 2hr

Cont.

- Once the patient is stable, look for a precipitating cause & treat it.
  - Usually infections or non – compliance to drugs
  - Others: trauma, infarction, drugs (cocaine, alcohol) etc.,
  - Ix: FHG, cultures, CXR, ECG
- Measure glucose 1 – 2 hrly., electrolytes (PO_4^{3-}, Ca^{2+}, Mg^{2+}), ABGs, anion gap 4hrly for the 1st 24 hrs.

Cont.

- Monitor BP, pulse, respiration, mental status and fluid input/output every 1 – 4 hrs.
- Ideally these patients should be in ICU or HDU; if in the ward, in the acute room
- PO_4^{3-} needs replacement only if < 0.32 mmol/L.
- Hypomagnesemia is rarely a problem but it may warrant replacement.

Prognosis

- Mortality is <5% if treated properly.
- Major complications:
  - Cerebral edema
  - Venous thrombosis
  - UGIB
  - ARDS

2. Hyperosmolar Non – ketotic Hyperglycemic Coma

- Usually a type II diabetic elderly patient living alone, no care, no food, unable to look after themselves
- They have mental confusion, lethargy or coma
- P/E reveals profound dehydration (***more severe than in DKA***), hyperosmolarity, hypotension, tachycardia & altered mental status
- May be precipitated by AMI or stroke. Others: pneumonia, sepsis or other serious infection

Cont.

- Sugars usually > 55.5 mmol/L; hyperosmolality > 350 mOSm/L; prerenal azotemia (high urea levels with minimally elevated creatinine).
- Na^+ normal or slightly low
- Acidosis or ketonemia is mild or absent

Cont.

- Treatment:
  - Soluble insulin
  - Rehydrate with N/S
  - Same treatment regimen will require more fluids and longer treatment
  - Social work: education & discussion with family.

Cont.

- If serum sodium is > 150mmol/L use 0.45% saline (otherwise NS is used).
- The water deficit should be replaced over 1 – 2 days at 200 – 300 ml/hr.
- Initially soluble insulin same as in DKA; then infusion of 3 – 7 units per hr. once sugars are < 14mmol/L reduce rate to 1 – 2 units/ hr.

Cont.

- Graduate as in DKA
- Discharge on intermediate insulin; Most go back with oral hypoglycemic agents (OHAs)
  - If the total dosage of soluble insulin is < 30 units/ day or if mixtard/ lente insulin is < 20 units, then the patient will do well on OHAs (biguanides e.g. metformin, sulfonylureas).

HYPOGLYCEMIC COMAS

- Signs and symptoms: fainting, confusion, palpitations, diaphoresis; cold and clammy skin
  - β – blockers mask signs and symptoms of hypoglycemia hence don't give a diabetic β - blockers.
- Dramatically recover on giving sugars, tea, food, IV 50% dextrose

Cont.

- Usually due to missing meals, while taking OHAs, overdosing, improvement & reduction of insulin requirements.
- Education of the patient: Carrying sugars around
- Withhold OHA, insulin
- Give dextrose infusion

4. MANAGEMENT OF COMPLICATIONS OF DM 4/4/2019

BY: DR. KUBO

Diagnosis – American Diabetes Association 2019

CRITERIA FOR THE SCREENING AND DIAGNOSIS OF DM		
	Pre – diabetes	Diabetes
HbA1C	5.7 – 6.4%	≥6.5%
FBS	5.6 – 6.9 mmol/L (100 – 124 mg/dL)	≥ 7.0mmol/L (126mg/dL)
OGTT	7.8 – 11.0mmol/L (140 – 199mg/dL)	≥11.1mmol/L (200mg/dL)
RBS		≥11.1mmol/L (200mg/dL)

Classification of complications

Acute complications

- Hypoglycemia
- DKA, HHS

Chronic complications

- Microvascular: retinopathy, nephropathy, neuropathy
- Macrovascular: CHD, cerebrovascular disease, PAD

1. HYPOGLYCEMIA

Management of hypoglycemia	
Asymptomatic: RBS < 3.9mmol/L	• Ingest CHO • Adjust medications
Symptomatic: RBS < 3.0 mmol/L) → manifests adrenergic & neuroglycopenic symptoms	• 15 – 20g of fast acting CHO (candy, sweetened juice, glucose tablets) • ***Patients on alpha glucosidase inhibitors e.g. acarbose, miglitol should take pure glucose (dextrose).***
Severe: bizarre behavior, unconscious, convulsions	• IV bolus of 50mls 50% dextrose (flash the line with NS to avoid thrombophlebitis) OR • IM/SC 1mg glucagon • Sugary fluid via NGT can be a last resort.

Don’t forget to determine & deal with the cause of hypoglycemia

- Excessive insulin dose e.g. ***in diabetic retinopathy, a patient may not be able to see the dose they are taking clearly.***
- Missed meal/ fasting
- Increased exercise
- Decreased insulin clearance e.g. in renal failure
  - 60% of exogenous insulin is cleared by the kidneys; the proportions are reversed for endogenous insulin. 40% of endogenous insulin is cleared by the kidneys. Progressively lower insulin doses in patients with diabetic nephropathy (CKD stages 3 – 4).

2. DKA

- Principles of management:
  - Fluid replacement
  - Insulin
  - Potassium repletion
  - Bicarbonate
  - Determination of precipitant
  - Watch out for complications of treatment

a. Fluid replacement

- The fluid deficit in DKA is usually 6L (9L in HHS).
- Initially, put at least 3 wide bore (green or gray) IV lines for: ***fluids***, ***insulin infusion & potassium supplementation***.
- Administer ***IV Normal Saline*** as follows:
  - 1L stat → 1L over 30 minutes. → 1L over 1 hr. → 1L over 2 hrs. → 1L over 4hrs.
- Catheterize the patient so as to ***monitor UOP.***
- ***Alternate with 5%D once the RBS is < 13mmol/L*** to prevent hypoglycemia.

b. Insulin

- Administer ***0.1U/kg IV bolus of soluble insulin stat.***
- Then: ***0.1U/kg/hr. infusion*** to normalize pH & for good glycemic control.
- Once acidosis has resolved (pH .35 – 7.45), ***revert to SC intermediate insulin***.
- Calculate total dose of insulin required & use this to calculate the 20 – am & 10 – pm dose.

c. Potassium repletion

- Total body potassium is usually depleted due to both ***renal*** & ***GI losses.***
- Replace as follows:

K^+ level (mmol/L)	**Administer this amount of KCl (mEq/L) over 4hrs. in fluids.**
4.5 – 5.5	10
3.5 – 4.4	20
< 3.5 (severe hypokalemia)	40 – 80

d. Bicarbonate

- **SHOULD ONLY BE CONSIDERED WHEN THE PH IS < 6.9.**
- Associated with ***cerebral edema***.

e. Determine the precipitant

- Inadequate insulin: poor compliance
- Infection (pneumonia, UTI, GE, sepsis)
- Infarction (Myocardial, cerebral, mesenteric)
- Drugs e.g. cocaine
- Pregnancy

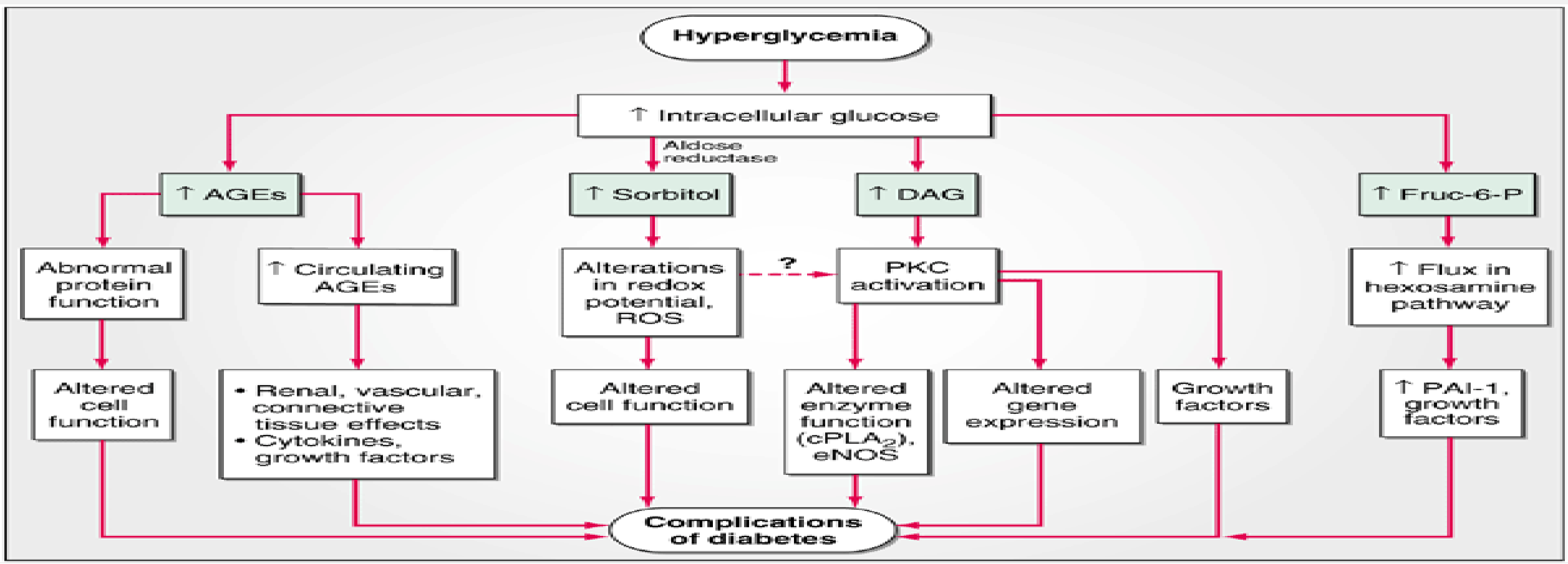
f. Watch out for complications of treatment

- Cerebral Edema
- Non – cardiogenic pulmonary edema

Management of chronic complications

1. Diabetic Neuropathy
2. Autonomic Neuropathy
3. Diabetic Retinopathy
4. Cardiovascular & Cerebrovascular disease
5. Diabetic Nephropathy
6. Diabetic Foot Ulcers

Possible molecular mechanisms of diabetes – related complications



PREVENTION: GOOD GLYCEMIC CONTROL!! (HBA1C < 7%)

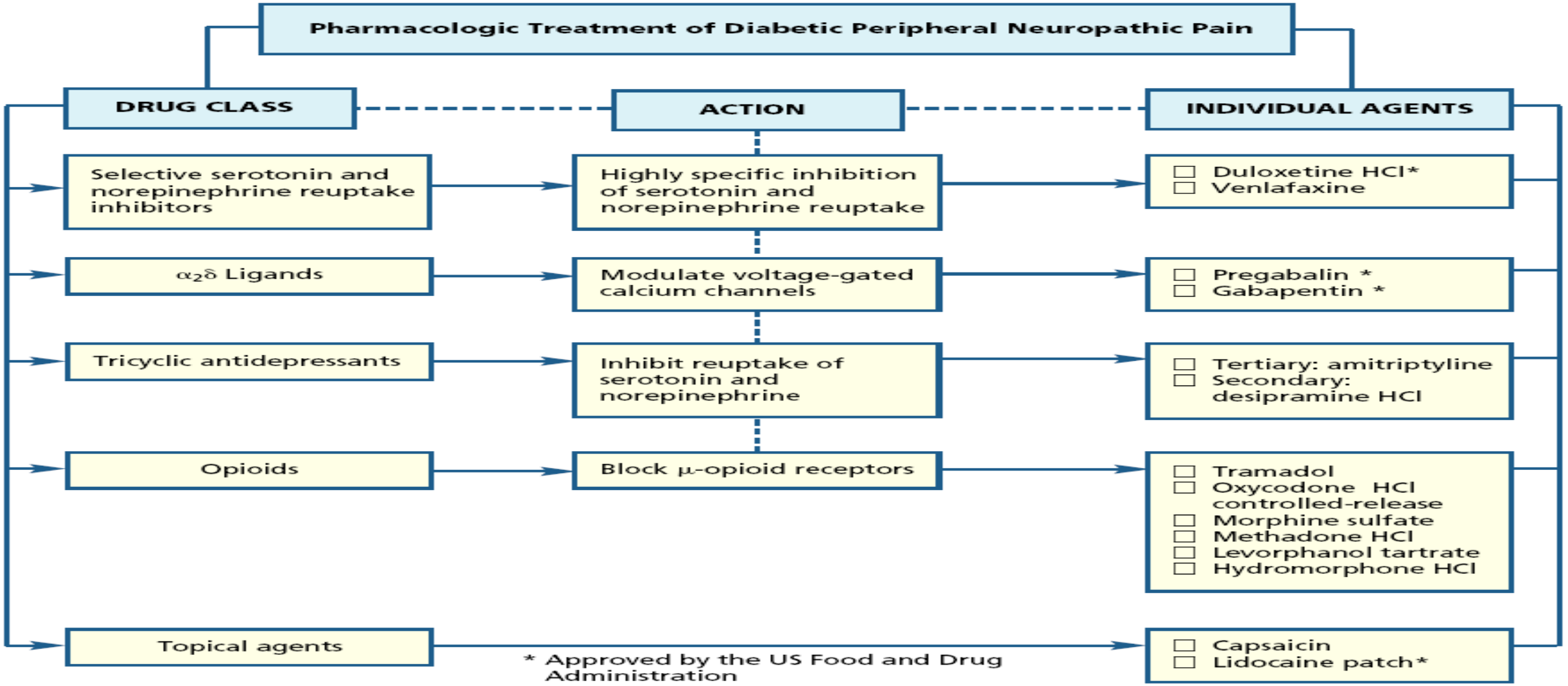
What is good glycemic control

TABLE 4. Summary of Glycemic Recommendations for Many Nonpregnant Adults With Diabetes

A1C	<7.0% (53 mmol/mol)*
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10.0 mmol/L)

**More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations. †Postprandial glucose may be targeted if A1C goals*

1. DIABETIC NEUROPATHY



TCAS

- ***Amitriptyline 25 – 100 mg*** usually used
- Onset of analgesia is in 1 – 4 weeks
- Administered nocte
- Has anticholinergic side effects: constipation, dry mouth, urinary hesitancy (avoid in an elderly male patient who most probably has concomitant BPH)

Gabapentin

- Dose 300mg day 1, 600mg day 2, 900 mg day 3
- Advantage: no significant DIs (good for polypharmacy)
- Disadvantages: can cause significant peripheral edema
- Require dose adjustment in renal impairment

Pregabalin

- Better BA compared to gabapentin
- Starting dose 50mg PO TID
- Side effects: dizziness, somnolence, edema

2. AUTONOMIC NEUROPATHY

- Clinical features: gastroparesis, urinary symptoms, diabetic diarrhea, erectile dysfunction, dyspareunia (due to vaginal dryness)
- Symptomatic:
  - Postural hypotension, gastroparesis, diabetic diarrhea, neuropathic bladder, ED, charcoat arthropathy, gustatory sweating
  - Subclinical abnormalities: abnormal pupillary reflexes, esophageal dysfunction, abnormal cardiovascular reflexes, blunted counter – regulatory responses to hypoglycemia

Management of gastroparesis: Prokinetics

- ***Metoclopramide*** PO 10mg QID, 30 minutes before meals
  - Increases gut motility through indirect cholinergic stimulation of gut muscle
  - A/E: tardive dyskinesia
- ***Domperidone*** (dopamine antagonist)
- ***Cisapride***
- ***Erythromycin*** interacts with motilin receptors, increasing gut motility
- Eat smaller, more frequent meals

Management of sexual dysfunction

- ED in males: PDE 5 inhibitors
- Females: vaginal lubricants, Rx. of vaginal infections, local or systemic estrogen replacement

Others.

- ***Diabetic diarrhea***: loperamide (opioid) or octreotide
- ***Diabetic Cystopathy***: timed voiding or self – catheterization +/- bethanechol (*direct acting cholinomimetic increases detrusor muscle contractility & relaxes sphincter*)
- ***Orthostatic hypotension***: fludrocortisone (mineralocorticoid, causes fluid retention; has action on alpha agonists), midodrine (alpha agonist), octreotide

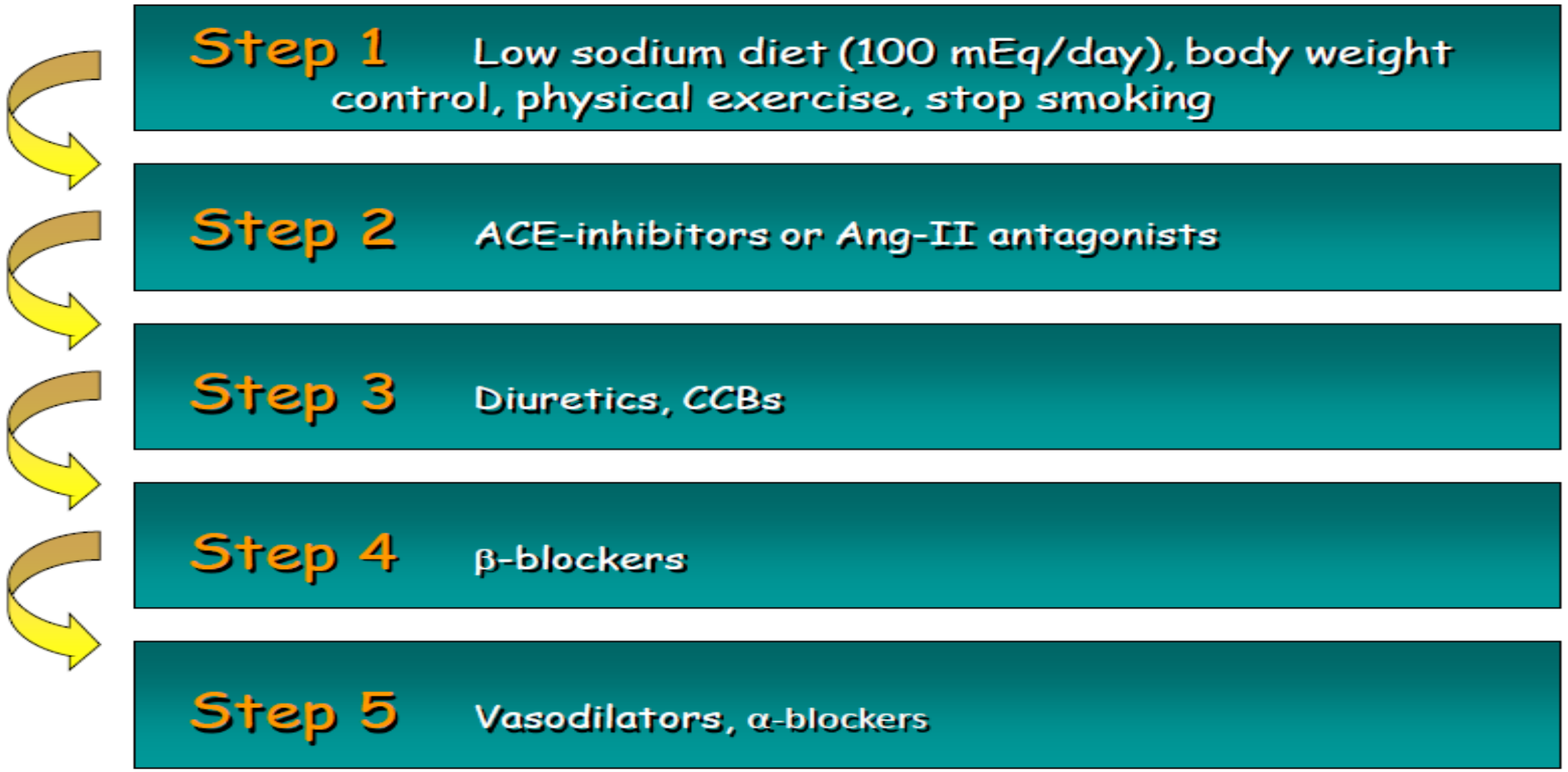
3. DIABETIC NEPHROPATHY

Interventions to Slow the Progression of Renal Disease in DM

INTERVENTION	TARGET
Blood-pressure control	<130/80 mm Hg
Inhibition of renin–angiotensin system	Urinary protein excretion, <0.3 g/24 hr
Correction of dyslipidemia	LDL cholesterol, <100 mg/dl (2.6 mmol/liter)
Glycemic control	Glycosylated hemoglobin, <7%

*Cessation of smoking, loss of weight, exercise, and reduction of protein, salt, and alcohol intake are also recommended, as appropriate. LDL denotes low-density lipoprotein.

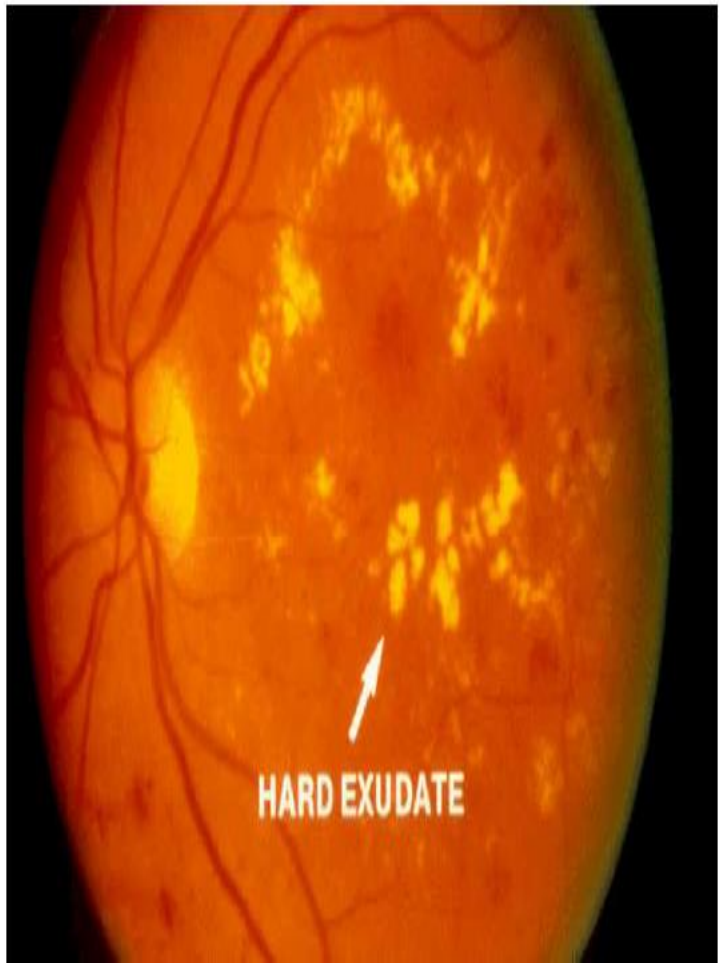
Intensive blood pressure control in diabetic patients



Goal treatment of HTN

- Lower target for diabetic patients (130/80 mmHg) than non – diabetic patients (140/90 mmHg).

4. DIABETIC RETINOPATHY



- Major classifications:
  - Proliferative
  - Non – proliferative
- Hard exudate: leakage
- Cotton wool spots: ischemia of nerve fibers

Management

- Most effective therapy is prevention
- Annual ophthalmology review for funduscopy
- Proliferative retinopathy: treated with ***pan – retinal laser photocoagulation***
- Macular edema: focal laser photocoagulation, intravitreal injection of anti – VEGF (bevacizumab).

5. CARDIOVASCULAR & CEREBROVASCULAR DISEASE

- Additional risk factors (deal with these well):
  - Accelerated atherosclerosis/ Dyslipidemia
  - Smoking
  - Obesity
  - HTN
  - Reduced physical activity
  - Micro- & macroalbuminuria
  - Abnormal platelet function
  - Insulin resistance

Management of dyslipidemia in DM

- DM is usually associated with hypertriglyceridemia & reduced HDL; +/- raised LDL
- Initial treatment: dietary changes
  - Increased monosaturated fat: olive oil, avocado
  - Reduced saturated fats & cholesterol
- Drug of choice: ***HMG CoA reductase inhibitors (statins)***
  - Pleiotropic effects: stabilize clots
  - Anti – inflammatory, antioxidant, plaque stabilizing effects

Anti – platelet therapy

Primary prevention

DM1 and DM2 patients ≥30 years with high CV risk

- CAD family history
- Smoking
- Hypertension
- Obesity
- Dislipidemia
- Albuminuria (micro or macro)

Secondary prevention

DM1 and DM2 patients with clinical history of cardiovascular disease

- myocardial infarction or angina
- Stroke or TIA
- Peripheral vascular disease
- By-pass surgery

aspirin (tablets)
75-100mg/day

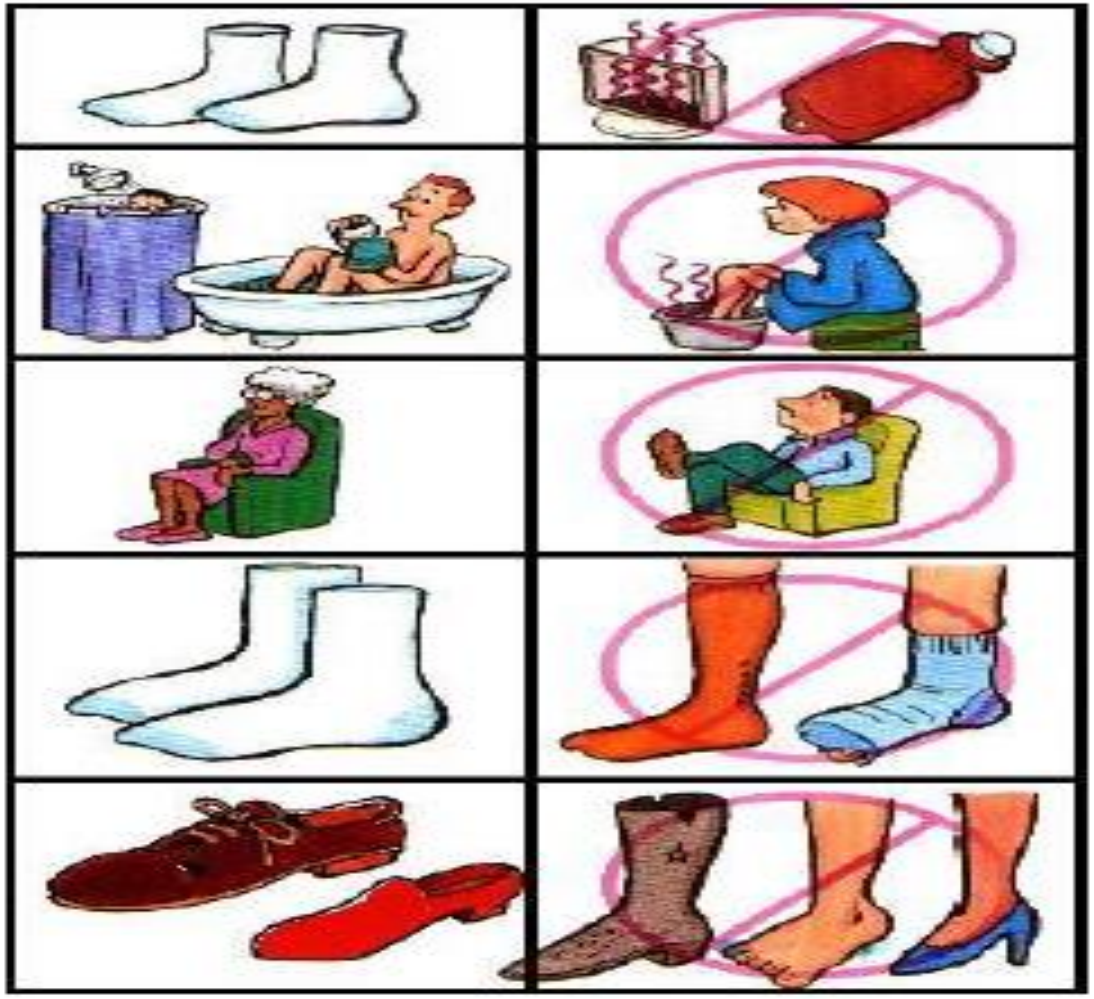
Contraindications

- Allergy
- Bleeding tendency
- Anticoagulation treatment
- Recent gastro-intestinal bleeding
- Clinically active liver disease
- Age ≤21 years (↑ Reye's syndrome)

clopidogrel
ticlopidine

6. DIABETIC FOOT ULCERS

Prevention



- Check feet daily
- Wash feet daily
- Keep toe – nails short
- Protect feet
- Always wear shoes
- Look inside shoes before putting them on
- Always wear socks
- Break in new shows gradually
- Use moisturizing lotions

Treatment of diabetic foot ulcers

- ***Off – loading***: complete avoidance of weight bearing on the ulcer, which removes the mechanical trauma that retards wound healing.
- ***Debridement***
- Appropriate ***antibiotics***
  - Mixed infections (cover both gram +ve & gram –ve anaerobes as mixed infection as usual)
  - Cephalosporin/ Augmentin/ clindamycin/ metronidazole/ fluoroquinolone
- Wound dressing
- Revascularization

5. MANAGEMENT OF HYPOTHYROIDISM 12/4/2019

BY: DR. GICHUHI

TYPED BY NAILA KAMADI

Causes:

1. Primary hypothyroidism
2. Transient hypothyroidism
3. Secondary hypothyroidism

Primary hypothyroidism

1. Autoimmune hypothyroidism: Hashimoto's thyroiditis
2. Iatrogenic causes: administration of RAI, post – thyroidectomy
3. Drugs: iodine excesses, iodine containing contrast media, anti – thyroid drugs
4. Congenital
5. Iodine deficiency

Transient hypothyroidism

- Silent thyroiditis
- Sub – acute thyroiditis
- After ^{131}I or sub – total thyroidectomy in Grave's disease
  - May be permanent or transient

Secondary hypothyroidism

- Hypopituitarism
- Hypothalamic disease

Cont.

- Most common cause: iodine deficiency
- Other common causes:
  - Autoimmune disease
  - Iatrogenic causes

Congenital hypothyroidism

- 1:4000 newborns
- MCC: ***thyroid dysgenesis*** (85% of cases)
- Clinical signs & symptoms are seen in < 10% of newborns.
  - Suspect in ***prolonged neonatal jaundice (MC symptom in neonates)***
  - Also: Hypotonia, Macroglossia, delayed bone maturation, umbilical hernia.

Cont.

- Permanent neurological damage if treatment is delayed or sub – optimal
- Neonatal screening: ***TSH*** or T_4
  - If TSH is high & T_4 is low, administer ***T_4 @ 10 – 16mcg/kg/dose*** & adjust dose using TSH levels.

Autoimmune hypothyroidism

- Classification

1. Hashimoto’s thyroiditis (enlarged goiter/ goitrous)
2. Atrophic thyroiditis (no enlarged goiter/ non – goitrous)

Laboratory diagnosis

- Measure ***TSH levels:***
  - If normal TSH: excludes primary hypothyroidism but not secondary hypothyroidism.
  - If high TSH: confirms primary hypothyroidism
- Measure ***T_4 levels***
- Measure ***thyroid peroxidase antibodies*** to confirm autoimmunity: usually high (*90 – 95% of patients*)
- If still in doubt: ***FNA***

Iatrogenic hypothyroidism

- Screen patients on anti – thyroid medication or who are post – thyroidectomy by measuring ***T_4 levels.***

Iodine deficiency

- Causes:
  - Inadequate iodine intake
  - ***Thiocyanates*** in cassava, cabbage and cigarettes which inhibit organification of iodine during synthesis of thyroid hormone
  - Selenium deficiency
- Management:
  - Thyroxine
  - Prevention is better → iodize food e.g. salt bread, single bolus of iodized oil in some countries.

Secondary hypothyroidism

- Usually other anterior pituitary hormones are also deficient.
- TSH levels are variable.
- T_4 levels: when low they confirm secondary hypothyroidism

Goals of therapy

- Amelioration of symptoms.
- Normalization of serum TSH
- Reduction in size of the goiter in patients with goitrous autoimmune thyroiditis (Hashimoto's disease)
- Avoidance of overtreatment (iatrogenic thyrotoxicosis)

Note

- When using thyroxine, about 50% of patients will have some decrease in goiter size. This lags behind the fall in TSH secretion.

Rx of hypothyroidism

- Treatment of choice for correction of hypothyroidism is ***synthetic hormone (T_4) thyroxine***
- Clinical hypothyroidism: use ***T_4 @ 1.6mcg/kg (~ 100 – 150mcg/day)***.
- If secondary to treatment of Grave's disease: ***~75 – 125mcg/ day***
- Adjust dose using ***TSH levels***
- Goal of Rx is to bring TSH on the lower half of the reference range.

Cont.

- TSH responses are slow
- Measure after ***6 weeks – 2 months***
- Clinical response is also slow
  - Signs of improvement within 2 weeks
- Clinical relief in 3 – 6 months after normal TSH levels are restored.

Cont.

- If the TSH remains high
- T_4 dose can be increased by ***12.5 to 25 mcg/d***
- Repeat TSH measurement in 6 weeks.

Other preparations that not recommended

- Desiccated animal thyroid preparations
  - Don’t have enough doses of thyroid hormone
  - Can cause allergic reactions
- Liothyronine (T_3)
  - More active form but requires more frequent dosing.
  - Can lead to adverse effects of excess thyroxine.

Long term monitoring of Rx

- Once TSH levels are in the lower half of the reference range of TSH, do ***TSH levels annually***; if patient is compliant increase interval to 2 – 3 yrs.
- If patient is requiring T_4 > 200mcg/d for euthyroidism, consider:
  - Poor compliance
  - Reduced absorption: if administered with cholestyramine, ferrous sulphate, antacids (aluminum hydroxide), calcium supplements etc.
  - Increased clearance: if co – administered with enzyme inducers e.g. rifampicin, carbamazepine, phenytoin

Cont.

- High doses also needed in:
  - Pregnancy
  - > 10% weight gain

Cont.

- If drugs that affect the absorption of T_4 are begun for co – existing medical conditions, serum TSH should be measured 6 weeks later.
- T_4 dose should be increased if serum TSH is high.
- Medications that interfere with T_4 absorption should be taken several hrs. after the T_4 dose.

Cont.

- Decreased in T_4 dose may be required in:
  - Normal aging
  - Weight loss of roughly >10% of body weight
  - Initiation of androgen therapy

Sub – clinical hypothyroidism

- High TSH with normal T_3 & T_4.
- No guidelines for Rx
- Options
  - Watchful waiting: patient may tip over to hypothyroidism
  - Low dose T_4: ~20 – 50mcg/d

Thyroid hormone in children

- When using thyroid hormone in children it may result in idiosyncratic ***pseudotumor cerebri*** that occurs months after therapy has begin.

Thyroid hormone in women of reproductive age & in pregnancy

- When a female patient is on thyroxine, they should plan their pregnancies hence advice on contraception. There is a risk of fetal neural maldevelopment.
- Monitoring TSH & T_4 in pregnancy (NB: pregnancy ref ranges different)
  - Every 4 weeks in 1st half of pregnancy
  - At least once between 26 – 32 weeks
  - 6 weeks after pregnancy: there may be a need to revert back to normal doses hence follow up is required.

Thyroid hormone in elderly patients

- Start on lower doses: 25 – 50 mcg/d every 6 weeks.
- Adjust dose by 25 mcg/d every 6 weeks.

Myxedema coma

- Hypothyroid condition with a high mortality rate even with best management.
- Triggers:
  - Impaired respiration: sedatives, anesthetic agent, pneumonia, MI
  - Sepsis
  - Exposure to cold temperature
  - Hypoglycemia
  - Hyponatremia

Signs & symptoms of hypothyroidism plus

- Reduced consciousness
- +/- seizures
- Hypothermia
- Respiratory depression

Management

- Administer IV T_4: 500 mcg LD then ~ 50 – 100 mcg/d OR
- IV T_3: 10 – 25 mcg BD or TDS OR
  - Since in myxedema coma, conversion of T_4 to T_3 is impaired
- Liotrix (T_4:T_3 → 200:25 mcg) stat then lower doses.

Supportive care

- Tailor to triggers
  - Sepsis: antibiotics
  - Hypoglycemia: glucose
  - Hypothermia: warm patient
  - Hypoventilation: support
- IV hydrocortisone: impaired adrenal reserve in most patients.

Thyroid preparations

- ***T_4***: half life of 7 days; administered PO; OD dosing; cheap; causes no allergy; monitor T_4 is possible.
- ***T_3***: half life of 24 hrs.; dose multiply; more active; more expensive; lab tests are not so reliable as it depends on what time the blood is taken (lab monitoring is difficult); avoid in elderly & those in cardiac disease ad can cause arrhythmias.
- ***Liotrix (T_4:T_3)***: expensive, not recommended in pregnancy
- ***Desiccated/ animal sources of thyroid***: varied hormone levels, allergenic, difficult to monitor levels in lab.

T_4 formulations

- Tablet (cheap), soft gel capsule
- Liquid formulation – only in Europe currently
- The soft gel capsule is an option:
  - If suspected poor absorption of tablet, esp. in the presence of atrophic gastritis.
  - Other option is to increase the dose of a T_4 tablet with monitoring of TSH (cheaper).

Timing of dose

- T_4 should be taken on an empty stomach with water, ideally an hr. before breakfast
- It should not be co – administered with medications that interfere with its absorption e.g. bile acid resins, calcium carbonate & ferrous sulphate

Cont.

- Plasma half life of T_4 is 1 week
- It takes approximately six weeks (6 half lives) before a steady state is attained after therapy is initiated or the dose is changed.

A/Es of thyroxine are rare

- Allergy is rare
  - Due to dye or excipients (filler) in the tablets
  - If due to dye use white 50mcg tablets
  - If due to excipients (except gelatin)
    - Use soft gel capsule (contains T_4 as a liquid)

Cont.

- Over – replacement with T_4 causes
  - Subclinical hyperthyroidism: normal T_4 & T_3 and low TSH
    - Risk of Atrial Fibrillation
    - Accelerated bone loss esp. in post – menopausal women (risk of fractures)
  - Overt hyperthyroidism

6. MANAGEMENT OF HYPERTHYROIDISM 16/4/2019

BY: DR. GICHUHI

TYPED BY NAILA KAMADI

Thyroid Hormone Synthesis

- Uptake of iodide → Oxidation of iodide to iodine mediated by peroxidase → iodine organification to form MIT & DIT → Coupling of iodotyrosine residues to form T_3 & T_4 mediated by peroxidase → Release of thyroid hormones → transport by TBG → Metabolism of thyroid hormones by deiodinase to T_3 & rT_3.

Causes

- Primary hyperthyroidism: e.g. by Graves' disease
- Secondary hyperthyroidism: TSH – secreting pituitary adenoma etc.

Graves Disease

- Clinical signs of thyrotoxicosis
- Ophthalmopathy (orbitopathy)
  - Characterized by: sensation of grittiness in the eye, excess tearing, Lid retraction, peri – orbital edema & proptosis
- Dermopathy
  - Usually on the lateral aspects of the lower legs.
  - Pre – tibial myxedema.
- Finger clubbing

Lab

- ↓ TSH
- ↑ T_3 & T_4

Clinical course

- Without Rx → 10 – 30% mortality
- Even on Rx, 15% of patients later progress to hypothyroidism after autoimmune destruction of the thyroid gland supervenes.
- Ophthalmopathy
  - This initially worsens from 3 – 6 months then spontaneously improves. During the period of worsening 5% of patients end up with ***optic nerve compression & corneal ulceration*** → **refer to ophthalmologist!**
- Dermopathy develops 1 – 2 yrs. after the diagnosis of hyperthyroidism & it may improve spontaneously.

Treatment

- Rapid amelioration of symptoms: Beta blocker
- Reducing thyroid hormone synthesis:
  - Anti – thyroid medication
  - Reducing the amount of thyroid tissue:
    - Radio – Active Iodine Therapy (RAIT)
    - Sub – Total Thyroidectomy

Anti – Thyroid Drugs

- Thioamides:
  - PTU
  - Carbimazole
  - Methimazole

PTU

- Not preferred unless in the 1st trimester of pregnancy.
- It is more (75%) protein bound hence doesn't cross the placenta significantly.
- Short half life of 1.5 hrs.
- Also used if there are **minor** reactions to Methimazole.
- ***Always given in divided doses***.

Cont.

- Carbimazole: used if Methimazole is not available
- Methimazole (***active metabolite of carbimazole***)
  - Preferred drug of choice
  - Long duration of action
  - Has low PPB & longer half life of 6h.
  - Initially dosed BD then once euthyroid → it is dosed OD.
  - Has lower incidence of side effects than PTU

Cont.

- Thioamides can be used:
  - Alone: for 1 – 2 yrs. hoping for remission or for long term therapy.
  - Used with RAIT
  - To control hyperthyroidism pre – operatively.

Pre – treatment evaluation when using Thioamides:

- Baseline
  - CBC + WBC differential → this is because Thioamides can cause agranulocytosis
  - LFTS: transaminases
- Thioamides are C/I when:
  - Absolute neutrophil count < 1000 cells/ μL
  - Elevated liver transaminases > 5X ULN

MoA of Thioamides

- Inhibit thyroid peroxidase (TPO)
- Inhibit organification & coupling of MIT & DIT to form T_3 & T_4
- Reduce thyroid antibody levels in Graves disease
- PTU also inhibits deiodination of T_4 to T_3

Dosing

- Methimazole
  - The starting dose varies according to the severity of hyperthyroidism. It ranges from ***5 – 40mg/d which is administered in divided doses*** that:
    - Normalize thyroid function faster
    - Have less GIT A/Es
  - Once euthyroid state is achieved, dosing is switched to OD.
- PTU: Doses range from ***100 – 200 mg TDS or QID.*** For PTU, the doses are always divided.

2 ways of administering the drugs:

1. Titration regime
   - Start at recommended dose then reduce dose as thyrotoxicosis improves. Therefore, lower maintenance doses are required.
2. Block – replace regime
   - Initial dose of Thioamides is ***maintained (which results in more A/Es***) then the patient is supplemented with T_4 to avoid drug induced hypothyroidism.
   - Not recommended.

Monitoring response to therapy

- Repeat TFTs every 3 – 4 wks.
- Adjust doses based on ***free T_4 levels***
  - Measure both T_4 & T_3 because T_3 can remain high even when T4 is suppressed
- TSH levels remain suppressed for many months
- Most patients are euthyroid after 6 – 8 wks. of Rx
  - ***Find out why***

Graves disease

- Remits in 18 – 24 months for 30 – 50% of patients
- Reduction in goiter may point towards possible remission
- An increase in the size of the goiter may denote treatment failure or hypothyroidism (i.e., over – treatment)
- Upon remission (i.e. normalized TSH levels for 12 – 18 mo. Coupled with reduced drug requirements), drugs can be tapered down then ultimately stopped. Follow – up is done for possible relapse annually.

Adverse Effects

- Common
  - Minor: rash, fever, arthralgia
  - Cross hypersensitivity is 50% between PTU & Methimazole

Cont.

- Rare major adverse effects: Stop treatment, never re – challenge & never use an alternative Thioamide. Include:
  - Hepatitis
  - SLE – like symptoms
  - Reversible agranulocytosis
    - S/S: warn patient of sore throat, fever, mouth ulcers; if these occur, stop drugs & do a CBC to establish if the symptoms are due to agranulocytosis.

Beta blockers: propranolol, atenolol

- Propranolol: 20 – 40mg QID
- Atenolol: 25 – 50mg OD
  - Preferred: OD dosed, beta 1 selective
  - Aim is to reduce pulse to < 90 mmHg if BP allows
- ***All beta blockers effectively diminish hyperthyroid symptoms but atenolol & propranolol are most commonly used.***

Cont.

- Adrenergic signs & symptoms that can be controlled by beta blockers include:
  - Tachycardia, tremor, palpitations, anxiety, stare & heat intolerance
- Incase of atrial fibrillation:
  - Thrombo – prophylaxis: warfarin
  - Digoxin: doses are higher due to faster drug metabolism

Radioiodine

- ^{131}I is used (10 – 15mCi) = millicuries
- Can be administered as a capsule or oral solution
- Emits beta particles that destroys the thyroid gland
- Half life is 5 days
- Anti - thyroid drugs should be stopped 3 – 5 days before RAI as they interfere with iodine uptake. Aim is thyroid ablation (not euthyroidism) then supplement with thyroid hormone
- Can be given as initial therapy or as an alternative when Thioamides fail to work.

Cont.

- Contraindications
  - Pregnancy
  - Breast feeding mothers
  - Children < 5 yrs.
- ***No decreased fertility, no increased risk of congenital malformations or cancer have been reported. RAIT is basically considered safe and can be used as a first line therapy***.

Cont.

- Avoided in severe orbitopathy:
  - Can cause it or make symptoms worse.
  - Severe orbitopathy may be avoided by using ***glucocorticoids.***
- RAI leads to hyperthyroidism 5 – 10 yrs. after administration hence monitor TFTs

Cont.

- At times, RAI may result in radiation thyroiditis 1 – 2 wks. After treatment presenting with mild pain at the thyroid gland.
- Symptoms of hyperthyroidism may persist for 2 – 3 months before effect of RAI takes place, in the mean time offer anti – thyroids
- In 6 months if patient is still hyperthyroid, considered failure of first RAI, give a 2nd dose there & then.
- Follow using TFTs annually, watch out for hypothyroidism then start supplementation with thyroid hormone.

Sub – total or total thyroidectomy

- Indications
  - Large goiter
  - Allergy to Thioamides
  - RAI is not possible
- Pre – operative
  - Control thyrotoxicosis: using anti – thyroid drugs
  - Potassium iodide (SSKI drops): reduces vascularity of tissue
  - Beta blockers

Complications of surgery

- Hyperparathyroidism
- Vocal cord paralysis due to RLN injury
- Hypothyroidism

In pregnancy

- Titration regime is used.
- PTU (75% PPB) esp. in the 1st trimester; less of drug crosses placenta, fetus won't have suppressed thyroid function
- Not carbimazole or Methimazole
  - Not PPB so can cross placenta
  - Congenital defects
    - Aplasia cutis
    - Choanal atresia
    - TOF

Cont.

- Monitor TFT
- In pregnancy TSH levels reduces and it may be possible to stop therapy
- It is rare to have neonatal thyrotoxicosis if mothers disease is controlled
- If neonatal has maternal antibodies; treat for 1 – 3 months until maternal antibodies have been excreted from the body

Adjunctive therapies

- Rarely used; cant be used alone
- Exception is iodine
  - Used for preoperative preparation
  - Treatment of severe hyperthyroidism or thyroid storm
  - Used after administration of RAI or with anti-thyroid drugs (not common)

Thyrotoxic crisis (thyroid storm)

- Rare
- Signs & symptoms of hyperthyroidism plus fever, delirium, seizures, coma, vomiting, diarrhea, jaundice
- Precipitated by: stroke, infections, trauma, DKA, surgical procedures esp. thyroidectomy, RAIT before control of hyperthyroidism

Management

- Supportive care
  - Monitor vitals
  - IVFs for diarrhea & vomiting
  - Cooling blankets & antipyretics for fever
  - Treat treatable precipitating causes
    - ABS for infection

Cont.

- Aim: reduction of thyroid hormone levels quickly
- Use large PTU doses (drug of choice) which inhibit TPO & prevent conversion of T4 to more active T3
- Potassium iodide:
  - Prevents thyroid hormone synthesis through ***Wolff – Chaikoff effect***;
  - Iodinated contrast media (iopodate, iopanoic acid) also inhibit conversion of T4 to T3 and are thought to inhibit thyroid hormone release
  - KI prevents uptake of iodide into gland
  - Iodide prevents synthesis of MIT & DIT

Cont.

- Propranolol
- Glucocorticoids:
  Dexamethasone

Ophthalmopathy

- **Mild to moderate disease**: no treatment is indicated. Usually there is spontaneous improvement. Characterized by:
  - Eye discomfort (dry sensation)
    - Artificial tears e.g. 1% methylcellulose
    - Dark glasses: reduced photo irritation of eyes
  - Periorbital edema: sleep in upright position; diuretics
  - Corneal exposure: tape eyelids shut when patient is asleep
  - Diplopia: offer special prismatic glasses to correct

Cont.

- Sever Ophthalmopathy
  - Optic nerve involvement, chemosis, corneal damage
  - Considered an emergency
  - Offer glucocorticoids (prednisone, methyl prednisone) +/- cyclosporine; short term benefit of reducing symptoms
  - Surgery is preferred: remove one of orbital walls to reduce pressure on optic nerve
  - Retro – orbital irradiation therapy

Cont.

- Dermopathy
  - No Rx is necessary
  - No surgery is necessary
  - Sometimes may cause cosmetic discomfort, may interfere with foot wear
  - Glucocorticoid ointments under occlusive dressings reduce symptoms.

Other medications used in hyperthyroidism

- Glucocorticoids
  - Used in thyroid storm
  - Inhibit peripheral T4 to T3 conversion
  - Reduce thyroid secretion
  - Efficacy is not well demonstrated
- Lithium
  - Blocks thyroid hormone release
  - Use limited by toxicity

Cont.

- Cholestyramine + Methimazole
  - Lowers T4 & T3 more rapidly than Methimazole alone
- Carnitine
  - A naturally occurring peripheral antagonist of thyroid hormone action
  - May be useful

Rituximab

- A monoclonal antibody that causes peripheral B cell depletion
- May induce remission than Graves; disease
- Slightly more expensive & adverse effects limit utility

Cont.

- Overt hyperthyroidism is associated with:
  - Osteoporosis
  - Risk of fractures
- For these patients: ingestion 1200 to 1500 mg elemental calcium daily through diet or supplements
  - Check calcium levels first; avoid in patients with hypercalcemia

7. HORMONE REPLACEMENT THERAPY

BY: DR. KUBO

TYPED BY NAILA KAMADI

If you’re helping someone & expecting something in return, ***you are doing business not kindness***.

- Anon.

6. RHEUMATOLOGIC THERAPEUTICS LEVEL VI MBCHB 2019

COMPILED BY NAILA KAMADI

OUTLINE

Management of Rheumatoid Arthritis

Treatment of acute & chronic gout

TREATMENT OF ACUTE & CHRONIC GOUT

19/2/2019

BY: DR. MUASYA

TYPED NAILA KAMADI

Introduction

- Gout is a familial metabolic disease
- It most often affects middle aged – elderly men & post – menopausal women
- It is characterized by recurrent episodes of acute & chronic arthritis due to deposition of **monosodium urate (MSU) crystals** in joints & cartilage.

Other associated features

- Formation of uric acid calculi in the kidneys
- Hyperuricemia
  - Uric acid is poorly soluble substance which is the major end product of purine metabolism.
- Tophi: hard deposits of crystalline uric acid & its fats in the skin, cartilage & joints
- Interstitial nephritis

Events which may precipitate an acute gouty arthritis

- Dietary excess
- Trauma
- Surgery
- Excessive ethanol ingestion
- Hypouricemic therapy
- Serious medical illnesses such as MI & stroke

Pathophysiology

- Urate crystals are initially phagocytosed by **synoviocytes**
- Synoviocytes then release inflammatory mediators (PGs, lysosomal enzymes, IL – 1)
- The inflammatory mediators attract & activate PMNL & mononuclear phagocytes (MNP), i.e., macrophages.
- The PMNL & MNP migrate into the joint space & amplify the ongoing inflammatory process.
- In the later phases of the attack, MNPs ingest urate crystals & release more inflammatory mediators.

Aims of Rx of gout

- Relieve the acute gouty attack
- Rx of chronic gout → urate – lowering therapy (Hypouricemic therapy) which aims to prevent:
  - Recurrent gouty attacks
  - Complications of gout (e.g. urate crystal formation)

A. TREATMENT OF ACUTE GOUTY ARTHRITIS

- The mainstay of Rx during an acute attack of gout is ***the administration of anti – inflammatory drugs s.a. Colchicine, NSAIDs or glucocorticoids*** depending on:
  - Age of patient
  - Other underlying illnesses

Cont.

- Both colchicine & NSAIDs may be poorly tolerated & dangerous in the elderly particularly in the presence of renal insufficiency & GIT disorders (some may have PUD).
- About 30% of elderly people have compromised renal system.
- In elderly patients with attacks involving 1 or 2 large joints ***intra – articular glucocorticoid injections*** may be preferred & effective.
- ***Ice pack applications*** (reduce the inflammatory process) & ***rest*** of the involved joints can be helpful.

NSAIDs in Gout

- These are the 1st line drugs for Rx of gout.
- Most often used in patients ***without complicating comorbid conditions.***
- NSAIDs given in ***full anti – inflammatory doses*** are effective in approximately 90% of patients & the resolution of signs & symptoms usually occurs in 5 – 8 days (~a week).

The most effective NSAIDs are those with a short half life including:

- Indomethacin 25 – 50mg TID
- Ibuprofen 800mg TID
- Diclofenac 50mg TID
- Naproxen 500mg BD (has a long half life)
- Celecoxib 800mg STAT then 400mg BD

Cont.

- COX – 2 selective inhibitors are thought to be equally effective but with less short – term GIT toxicity
  - Remember COX – 2 selectivity is relative rather than absolute; with increasing doses of drugs, there may be mild COX – 1 inhibition.
- All other NSAIDs except ***aspirin, salicylates*** & ***tolmentin*** have been used successfully used to treat acute gouty episodes
  - Read about the effect of low dose & high dose salicylates on uric acid excretion.
- ***Oxaprozin*** lowers serum uric acid and should not be given to patients with uric acid stones because it increases uric acid excretion in the urine.

MoA of NSAIDs in gout

- Inhibition of prostaglandin synthase (COX)
- Inhibit urate crystal phagocytosis

Colchicine

- When given orally it is effective treatment if ***used early in the attack***.
- 1 – 2 0.6 mg tablets can be give every 6 – 8hrs. over several days with subsequent tapering once a good anti – inflammatory effect is achieved.
- Colchicine ***must be stopped promptly at the 1st sight of loose stools*** & symptomatic Rx must be given for the diarrhea.

Cont.

- IV colchicine is occasionally used e.g. for pre - & post – operative prophylaxis in 1 – 2 mg doses when patients cannot take medications orally
  - Generally IV use is discouraged (FDA warning)
- Life – threatening colchicine toxicity & sudden death have been reported with the administration of > 4mg/day IV. Limit to 1 or 2 doses then use other measures.

Cont.

- The IV colchicine should be given slowly over 10 minutes in a solusate/ infusion set through an established IV line
- The total doses should ***never >4mg.***

Glucocorticoids

- Oral glucocorticoids s.a. prednisone at 30 – 50 mg/d as the initial dose & gradually tapered off with the resolution of the attack can be effective in ***polyarticular gout.***
  - Usually Start with NSAIDs, colchicine then graduate to glucocorticoids if not getting good response.
- For single or few involved joints ***intraarticular triamcinolone acetonide 20 – 40mg or methylprednisolone 25 – 50mg*** have been effective & well tolerated.
  - Read about: why triamcinolone & methylprednisolone are used.

Interleukin – 1 inhibitors

- New drugs targeting IL – 1 s.a. **anakinra**, **canakinumab** & **rilonacept** are used in the Rx. Of gout
- Data is currently limited.
- However, these drugs may provide a promising treatment options for acute gout in patients with C.I to or who are refractory to traditional therapies like NSAIDs or colchicine.

Cont.

- **Canakinumab** is a fully human anti – IL – 1β MAB
- It can provide rapid & sustained pain relief at a dose of 150mg SC.
- IL – I inhibitors are also being evaluated for prevention of gout flares while initiating urate lowering therapy.

B. TREATMENT OF CHRONIC GOUT: HYPOURICEMIC THERAPY

- Ultimate control of gout requires correction of the basic underlying defect, i.e., hyperuricemia.
- Hypouricemic regimens attempt to normalize serum uric acid to < 300 – 360mmol/L (5.0 – 6.0mg/dL) to prevent recurrent gouty attacks & eliminate tophaceous deposits (ref. 2nd aim of Rx in gout)
- These medications are generally required for life.

Cont.

- Hypouricemic therapy should be corrected when hyperuricemia cannot be corrected by simple means s.a.:
  - Control of body weight
  - Low purine diets
  - Increased liquid ingestion
  - Limitation of ethanol intake
  - Avoidance of diuretic use

Cont.

- The decision to initiate Hypouricemic therapy is usually made by taking into consideration:
  - Number of acute attacks (urate lowering may be cost effective after 2 attacks)
  - Serum uric acid levels (progression is more rapid in patients with serum uric acid >535 mmol/L (>9mg/dL)
  - Patients willingness to commit to lifelong therapy or
  - Presence of uric acid stones
    - Urate lowering therapy should be initiated in any patient who already has tophi or chronic gouty arthritis

There are 2 categories of Hypouricemic drugs:

Uricosuric drugs

- These increase excretion of uric acid & therefore reduce the concentrations in plasma.

Xanthine Oxidase Inhibitors (XOIs)

- Reduce the synthesis of uric acid by inhibiting XO the enzyme involved in the terminal steps of the biosynthesis of uric acid
- Include: Allopurinol, Febuxostat, PEGylated uricase.

Uricosuric agents

- **Probenecid** & **sulfinpyrazone** are uricosuric drugs used to decrease the body pool of urate in patients with tophaceous gout or in those with increasingly frequent gouty attacks.
- Uricosuric agents should not be used in patients who excrete large amounts of uric acid because they can precipitate the formation of uric acid calculi → obstructive uropathy → AKI

Cont.

- Uricosuric agents can be used in patients with good renal function who under – excrete uric acid, with <600 mg in a 24 – h urine sample.
- Urine volume must be maintained by ingestion of ≥ 1.5l or more of water in a day.

Cont.

- **Probenecid** can be started at 250mg BD & increased gradually as required up to 3g in order to maintain a serum uric acid level of <300mmol (5mg/dL)
- **Probenecid** is generally not effective in patients with serum creatinine levels of >177mmol/L (2mg/dL)
  - These patients may require **allopurinol or benzbromarone**, a uricosuric drug that is more effective in patients with renal failure.

Cont.

- Losartan, fenofibrate & amlodipine also have mild uricosuric effects.
- Used in hypertensives or if patients require anti – lipidemic therapy.

XOIs

- Include:
  - Allopurinol
  - Febuxostat
  - PEGylated uricase.

Allopurinol

- Is the MC used Hypouricemic agent
- It is the best drug to lower serum urate in:
  - Overproducers
  - Urate stone formers
  - Patients with renal disease

Cont.

- It can be given in a single morning dose, 100 – 300mg initially & increasing up to 800mg if necessary
- In patients with chronic renal disease, the initial allopurinol dose should be lower and adjusted depending on the serum creatinine concentration.

Cont.

- Patients with frequent acute attacks may also require lower initial doses to prevent exacerbations.

Cont.

- Toxicity of allopurinol has been recognized increasingly in:
  - Patients with renal failure who use thiazide diuretics
  - Patients allergic to penicillin & ampicillin

A/Es of allopurinol

- The most serious A/Es include:
  - Skin rash with progression to life – threatening TEN
  - Systemic vasculitis
  - BM suppression
  - Granulomatous hepatitis
  - Renal failure

Cont.

- Patients with mild cutaneous reactions to allopurinol can either:
  - Reconsider the use of a uricosuric agent
  - Attempt desensitization to allopurinol
  - Take Febuxostat
  - They can also pay increased attention to diet

Febuxostat

- A non – purine inhibitor of xanthine oxidase
- All of the drug & its metabolites appear in urine
  - < 5% of drug is excreted unchanged in urine
- No dosage adjustment is necessary in patients with mild – moderate renal impairment.

Cont.

- Febuxostat is a potent & selective inhibitor of XO
  - It therefore reduces the formation of xanthine & uric acid
- At a dose of 80 – 120 mg OD it is more effective than allopurinol at a dose of 300mg daily in lowering serum urate levels
- It is more efficacious & more potent

A/E

- As with allopurinol, prophylactic Rx with colchicine or NSAIDs should start at the beginning of Rx to avoid gouty flares
- The most frequent Rx related A/Es are liver function abnormalities, diarrhea, headache & nausea
- Febuxostat appears to be well tolerated in patients with a history of allopurinol intolerance

Pegloticase

- It is the newest urate – lowering therapy to be approved for the Rx of refractory chronic gout
- It is a recombinant form of the enzyme **urate oxidase** or uricase (it is PEGylated uricase)

Mechanism of Action

- Converts uric acid to allantoin a water soluble non – toxic metabolite that is excreted primarily by the kidneys.

Clinical use

- Indicate for patients with gout who fail Rx with standard therapies s.a. XOIs.
- It is administered IV usually at 8mg every 2 weeks.
- It can dramatically lower serum uric acid in up to 50% of such patients..

Cont.

- Urate lowering drugs are generally not initiated during acute attacks but after the patient is stable & low dose colchicine has been initiated to decrease the risk of flares that occurs with urate lowering drugs
- Colchicine prophylaxis in doses of 0.6mg OD or BD is usually continued together with the hypouricemic agents until the patient is normouricemic & without gouty attacks for 6 months or as long as tophi are present.

Cont.

- Colchicine should not be used in dialysis patients.
- It is given in lower doses in patients with
  - Renal disease or
  - Those using P glycoprotein or CYP3A4 inhibitors s.a. clarithromycin that can increase toxicity of colchicine

TYPED NAILA KAMADI

Nothing can dim the light that shines from within ☺.

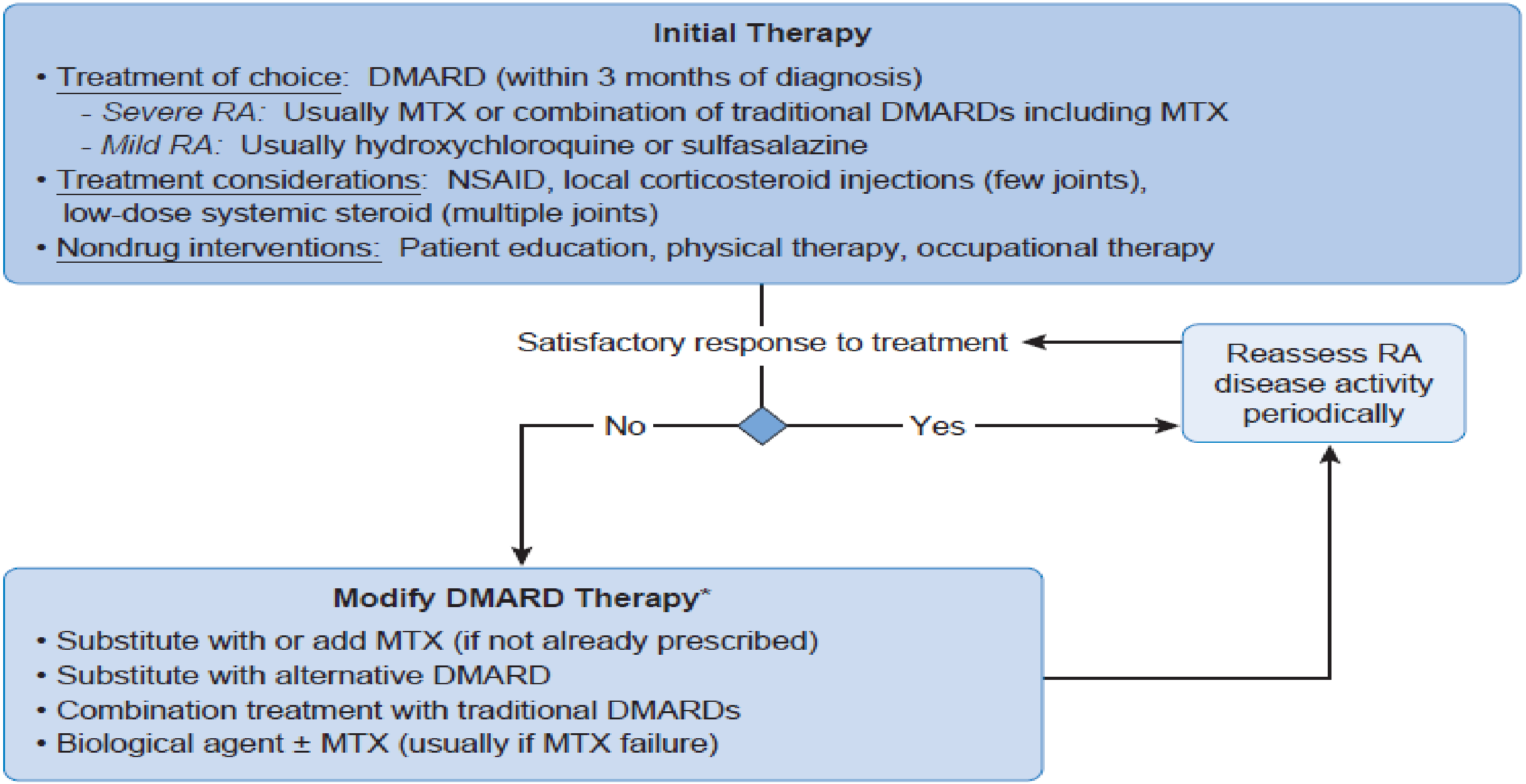
By Dr. Jane Gacheru

#Jesus_Is_Lord

MANAGEMENT OF RHEUMATOID ARTHRITIS

5th/3/2019

BY: DR. EZZI


Initial Therapy
• Treatment of choice: DMARD (within 3 months of diagnosis)
- Severe RA: Usually MTX or combination of traditional DMARDs including MTX
- Mild RA: Usually hydroxychloroquine or sulfasalazine
• Treatment considerations: NSAID, local corticosteroid injections (few joints), low-dose systemic steroid (multiple joints)
• Nondrug interventions: Patient education, physical therapy, occupational therapy
Satisfactory response to treatment
No
Yes
Reassess RA disease activity periodically
Modify DMARD Therapy*
• Substitute with or add MTX (if not already prescribed)
• Substitute with alternative DMARD
• Combination treatment with traditional DMARDs
• Biological agent ± MTX (usually if MTX failure)

NSAIDs

- Provide rapid pain relief and reduction of joint inflammation.
- No NSAID of choice
- Selection based on
  - Patient preference
  - Convenience
  - Cost
  - Safety

NSAIDs

- 2 week trial at moderate dose on a scheduled basis (anti-inflammatory efficacy)
- Non aspirin NSAIDs are preferred

NSAIDs

- Differentiating properties
  - Indomethacin: CNS penetration (CNS A/E)
  - Piroxicam: PUD, GIT bleeding
  - Celecoxib, high dose ibuprofen, diclofenac: MI
  - Naproxen: Best CVS safety
  - Diclofenac, meloxicam, indomethacin: Thrombosis
  - Aspirin: GIT toxicity

Traditional DMARDs

- Every RA patient should receive DMARD
- Initial selection based on:
  - Disease activity (low, moderate-high)
  - Prognostic findings
  - Disease duration.

Traditional DMARDs

- MTX, LEF initially chosen (good clinical response)
- Treat with at least one DMARD + NSAID + low dose oral corticosteroids (PRN)
- NSAIDs + corticosteroid discontinue (disease remission)
- DMARDs discontinuation - Rebound flare (indefinitely)

Hydroxychloroquine

- 1st line for mild to moderate RA
- Add to MTX
- Safe in pregnancy

Cont.

- 2/3rd respond favourably
- Benefits within 4 months of therapy
- Well tolerated
- C/I: Renal impairment

Hydroxychloroquine

- Most serious toxicity – retinal damage (rare)
- Risk increased:
  - High cumulative doses
  - Increased age (*>60 years)*
  - Liver disease
  - Retinal disease

Hydroxychloroquine

- Immediately stop therapy
- Undergo ophthalmologic evaluation: retinal pigmentation
- Routine eye examination:
  - High risk for retinal damage
  - Renal dysfunction
  - HCQ therapy for >10 years

Sulfasalazine

- 1st line for mild to moderate RA
- Add to MTX
- Safe in pregnancy
- Effects apparent within a month
- Clinical response after 3 months (adjust dose later)

Sulfasalazine

- Adverse effects:
  - GIT discomfort
  - Dizziness
  - Skin rashes
  - Hematologic effects:
    - Leukopenia, thrombocytopenia, agranulocytosis
    - Routine CBC
  - Hepatitis (rare, serious)
- Minimize by starting low dose, weekly adjustment

Gold Compounds

- Parenteral preparations:
  - Gold sodium thiomalate (aqueous solution)
    - Easier to administer
    - Frequent side effects
  - Aurothioglucose (oil suspension)
    - Risk of nephrotoxicity

Gold Compounds - Toxicities

- Aurothioglucose:
  - Renal toxicity:
    - Membranous nephropathy
    - Nephrotic syndrome
    - Interstitial nephritis
  - Thrombocytopenia
  - Aplastic anemia
- Auronofin:
  - Diarrhea

Methotrexate

- Recommended as initial DMARD
- Potent DMARD
- Rapid onset (1 month)
- High efficacy rate

Methotrexate - Dosing

- Given orally as weekly dose
- Increase dose after every 2 months if no response
- If unresponsive:
  - Maximum 25mg/week
  - Give subQ or IM (more effective)
  - Add/ Substitute another DMARD

Methotrexate – Adverse Effects

- Common:
  - GIT distress
  - Mucositis
  - Dizziness
  - Mild alopecia
- Severe:
  - Myelosuppression
  - Pneumonitis
  - Hepatic fibrosis, cirrhosis
- Renal dysfunction result in accumulation
- Pregnancy X

Methotrexate – Folate/Folinic Acid

- Folate supplementation reduces A/E (GIT distress, mucositis, LFT elevation)
- Higher MTX dose (folate antagonist)
- Folic acid:
  - Simpler
  - Inexpensive

Methotrexate – Drug Interaction

- NSAIDs increase MTX concentration
- Trimethoprim increase risk of myelosuppression
- MTX + LEF increase risk of hepatitis

Leflunomide

- Similar efficacy to MTX
- Clinical response in 4 weeks
- Can substitute/add to MTX

Leflunomide - Dosing

- Active metabolite responsible for pharmacologic activity
- Half life of 2 weeks (loading dose)

Leflunomide – Adverse Effects

- Diarrhea
- Rash
- Alopecia
- Hepatitis
- Pregnancy X

Leflunomide - Elimination

- 2 years for metabolite to be undetectable
- Cholestyramine enhances elimination:
  - Planning family
  - Hepatotoxicity
  - Overdose
- Alternative is activated charcoal

Minocycline

- Useful adjunctive agent
- Immunomodulatory and anti-inflammatory effects

Azathioprine

- Approved for severe RA
- Adverse Effects:
  - GIT intolerance (most common)
  - Myelosuppression
    - Reversible
    - Increased risk with renal failure
- Allopurinol increase toxicity (decreases elimination)

D-Penicillamine

- Outdated (lengthy dose titration, toxicity)
  - 6 months before therapeutic benefit
  - Rash, stomatitis, dysgeusia
  - Thrombocytopenia
  - Proteinuria
  - Renal toxicity
  - Autoimmune syndromes (SLE, myasthenia gravis, polymyositis, Goodpasture syndrome)

Combination Therapy

- Associated with improved outcomes
  - Different pharmacological or site of action
  - Lower doses of individual drugs

Combination Therapy

- Examples;
  - MTX + HCQ (mod – high)
  - MTX + LEF (high)
  - MTX + SSZ (poor prognosis)
  - HCQ + SSZ (good prognosis)
  - MTZ + HCQ + SSZ (poor prognosis)

Biologic Agents

Biologic agents

- TNF – alpha blockers: adalimumab, infliximab, certolizumab, golimumab, Etanercept
- Abatacept: inhibits T cell activation & binding to APCs
- Rituximab: targets CD20+ve B cells
- Tocilizumab Humanized anti – IL – 6 receptor antibody
- Anakinra
- Rilonacept
- Canakinumab

Etanercept

- Uses:
  - Moderate – severe RA with/ without MTX
  - Juvenile RA
  - Ankylosing spondylitis
  - Psoriatic arthritis, plaque psoriasis.
- Soluble TNF receptor that binds TNF (inactivation)
- Given SC (response in 2 weeks)

Etanercept – Adverse Effects

- Injection site reactions
- URTI
- Development of autoantibodies (ANA, dsDNA)
- CHF exacerbation
- Lymphoma
- Serious infections (Immunosuppression)
  - Sepsis
  - TB, Mycobacterial
  - Fungal

Infliximab, Adalimumab

- Infliximab:
  - Chimeric IgG antibody against TNF
  - Used for:
    - Crohn's disease, ulcerative colitis
    - Ankylosing spondylitis
    - Psoriatic arthritis, plaque psoriasis
    - Moderate – severe RA,
  - Given IV
  - Given with MTX to prevent antibodies to infliximab

Infliximab, Adalimumab

- Adalimumab:
  - Humanized IgG1 monoclonal antibody
  - Given subQ

Infliximab, Adalimumab - Adverse Effects

- Similar to etanercept
- Antibodies to infliximab, adalimumab

Certolizumab, Golimumab

- Similar efficacy
- Certolizumab:
  - Pegylated Fab portion
  - Used for:
    - Moderately to severely active RA
    - Crohn’s disease
  - Half life of 2 weeks (monthly)

Certolizumab, Golimumab

- Golimumab:
  - Human IgG1 monoclonal TNF α antibody
  - binds to soluble & transmembrane TNF
  - Used for:
    - Moderate to severe active RA (with MTX)
    - Psoriatic arthritis
    - Ankylosing spondylitis.

Certolizumab, Golimumab – Adverse Effects

- Well tolerarated
- Similar safety profiles to other anti-TNF agents.
- Certolizumab:
  - Urinary tract infections

Anakinra

- IL-1 receptor antagonist
- Given daily subQ
- Adverse Effects:
  - Injection site reaction
  - Neutropenia, severe infections
- Not combined with anti-TNF
- Less effective than anti-TNF

Abatacept

- Selective costimulation inhibitor of T-cell activation
- Not combined with TNF antagonists
- Adverse Effects:
  - Infections: pneumonia, cellulitis, UTI, pyelonephritis
  - Malignancy
  - Exacerbates COPD

Rituximab

- Chimeric monoclonal antibody binds to CD20 on B cells
- Adverse effects:
  - Infusion reactions
    - Premedicate with IV methylprednisolone
  - Serious infections

Tocilizumab

- Humanized anti-IL-6 receptor antibody
- Not combined with anti-TNF
- Adverse Effects:
  - Severe infections: TB, pneumonia, herpes zoster
  - GIT perforation (diverticulitis)
  - Neutropenia, thrombocytopenia
  - Increased liver enzymes, lipid abnormalities
  - Hypertension

Corticosteroids

- In unremitting disease
- Lowest effective dose for shortest duration
- Rapid onset of action
- Taper down
- Provide bridge therapy until DMARDs become effective.

Corticosteroids - Dosing

- Give intermediate or short acting
- Given BD (divided dose)
  - Anti-inflammatory effect dampens after 12 hours
- If OD, give in evening
  - Proinflammatory surge at night

Steroid Induced Osteoporosis

- Chronic therapy
- Inhibits bone formation, enhances bone resorption
- Prevention & Treatment:
  - Ca^{2+}, vitamin D (maintain Ca^{2+} balance)
  - Bisphosphonates
  - HRT
  - Thiazide diuretics (hypercalciuria)

Intra-articular Steroids

- Safe and effective
- One or few joints (temporary flare)
- Minimal systemic side effects
- Immediate onset of action but short lived

7. GASTRO – HEPATO – BILIARY THERAPEUTIC NOTES
LEVEL VI MBCHB
2019

COMPILED BY NAILA KAMADI

OUTLINE

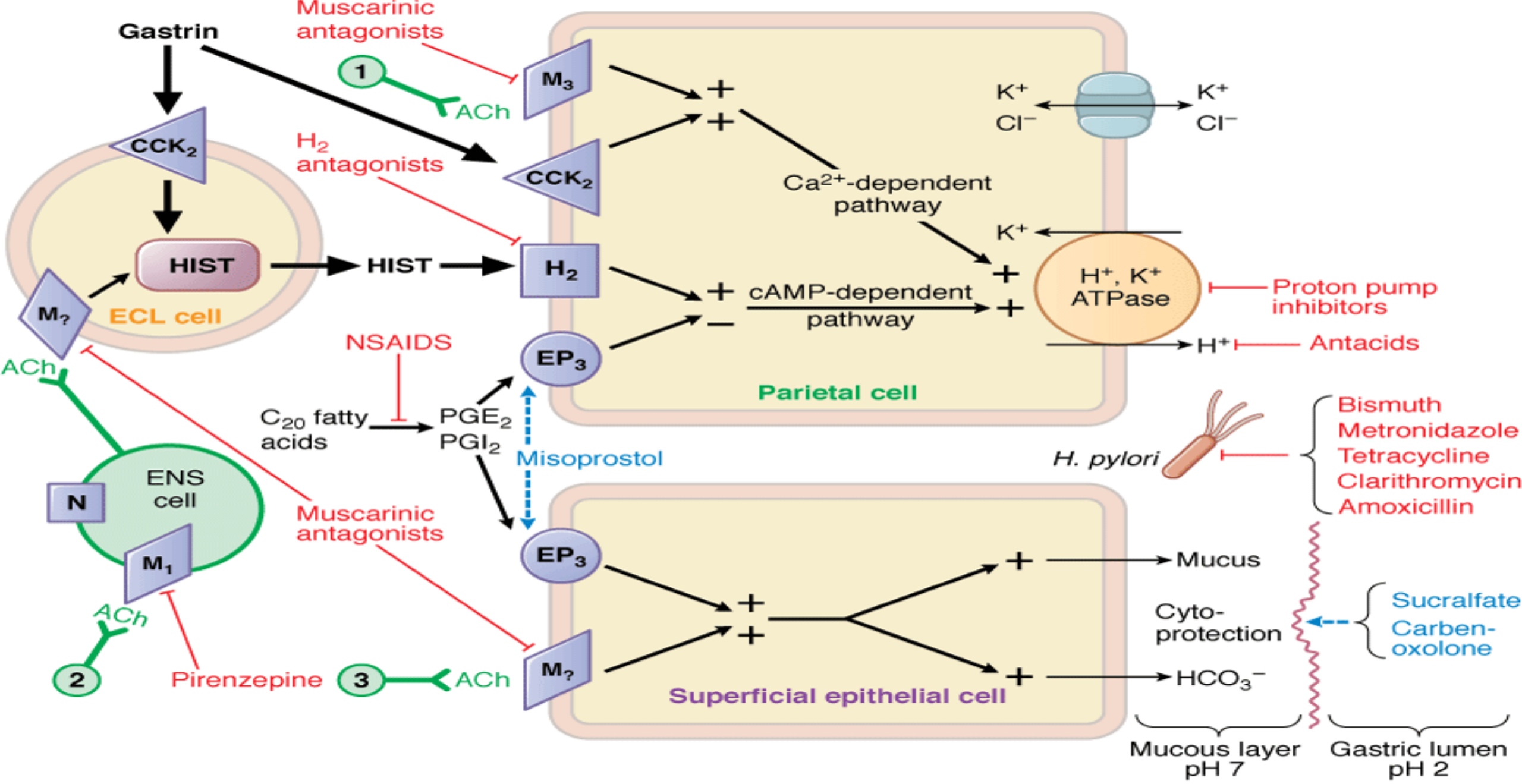
- Management of acute & chronic diarrhea
- PUD
- Portal HTN & Upper GI Bleeding
- Chronic Liver Disease
- Parenteral Nutrition

1. MANAGEMENT OF ACUTE & CHRONIC DIARRHEA

BY: DR. MUASYA

2. DRUG TREATMENT OF PEPTIC ULCER DISEASE (PUD)

5/2/2019



Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com
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1. PUD

- When a patient presents with PUD, check for the following on history:
  - Drug history:
    - NSAIDs → inhibit the gastro – protective prostaglandins
    - Low dose aspirin → anti – platelet effect
  - Medical history of *H. pylori* infection.
- When accompanied by severe bleeding, the most common scenario is a **posterior wall ulcer** eroding into the **gastroduodenal artery.**

Cont.

- Most cases stop spontaneously but 20% continue bleeding.
- Generally, medical management is achieved by:
  1. Proton Pump Inhibitors
  2. H_2 Receptor Antagonists (H_2RA)
  3. Somatostatin

Proton Pump Inhibitors Include:

- Omeprazole
- Rabeprazole
- Esomeprazole
- Lansoprazole
- Pantoprazole

H_2 Receptor Antagonists (H_2RA)

- Cimetidine
- Ranitidine
- Famotidine
- Nizatidine

Cont.

- Omeprazole: IV bolus 80 mg, followed by 8mg/ hr. infusion for 72 hours.
- Then 40mg BD for 2 weeks.
- ↓ recurrence & need for surgery.
- Follow with prompt endoscopy esp. those with **ALARM Symptoms**

Beware of ALARM Symptoms

- A – anemia
- L – loss of weight
- A – anorexia
- R – recent onset/ progressive symptoms
- M – melena stool/ hematemesis
- S – swallowing difficulty

Helicobacter pylori – Related PUD

Goal of Therapy

- Render the patient asymptomatic
- Heal the ulcer
- Eradicate the infection (eradication rate ≥80%)
- Cure the disease
- Treatment must be effective, well – tolerated, easy to comply with & cost – effective.

Primary Treatment

- Triple therapy:
  - PPI + clarithromycin + amoxicillin/metronidazole
  - Amoxicillin is preferred due to fewer side effects.
  - Duration of treatment ➔ 14 days.
  - BD dosing for PPI

Primary Treatment

- Quadruple therapy:
  - Bismuth salt + metronidazole + tetracycline + PPI/H_2RA
  - Complex & has ↑ side effects
  - The PPI permits a shorter duration of treatment (10 days)

Primary Treatment

- Sequential therapy:
  - PPI + Amoxicillin (5 days) then PPI + clarithromycin + imidazole (5 days)
  - Superior but complex
  - Initially treat with least resistant antibiotic (↓ bacterial load)

Drug Substitutions

- For penicillin allergies use:
  - Metronidazole in triple therapy
  - Quadruple therapy
  - Sequential therapy not recommended
- Others:
  - One PPI is substituted for another
  - PPIs & H_2RA can be substituted
  - Clarithromycin can be substituted for tetracycline in quadruple therapy

Secondary (Rescue) Therapy

- Second line regimens:
  - Avoid initial antibiotics
  - Use antibiotics with least resistant
  - Drugs with topical effect (bismuth)
  - 14 day treatment duration
- Quadruple therapy is mostly used as a 2nd line

Secondary (Rescue) Therapy

- Rifabutin:
  - For Clarithromycin/ metronidazole resistance
  - Last option
  - Multiple eradication failures
  - Expensive
  - Major hematologic side effects

Patient Education

- Antibiotics:
  - Nausea, abdominal pain, diarrhoea.
  - *C. Difficile* - associated diarrhoea
  - Oral, vaginal candidiasis
  - Taste disturbance: clarithromycin, metronidazole
  - Disulfiram like reaction (metronidazole)
  - Photosensitivity, tooth discoloration (tetracycline)

Patient Education

- PPI:
  - 30 – 60 minutes before meal
  - Long – term: risk of osteoporosis
- Bismuth salts: Darkening of the tongue & stool.
- Drug Interactions:
  - Metronidazole & clarithromycin (are CYP inhibitors)

NSAIDs – Induced PUD

Mechanism of NSAID induced ulceration

- Topical irritant effect of the drugs on the mucosa
- Impairment of barrier properties of the mucosa
- Suppression of prostaglandin synthesis
- ↓ of gastric mucosal blood flow
- Interference with the repair of superficial injury

Treatment

- Discontinue NSAIDs (low dose aspirin)
- PPI:
  - Preferred for ulcer healing (4 weeks)
  - Potent acid suppression
  - Symptom relief
  - Extend to 12 weeks if continuing NSAIDs

Reducing Risk of NSAIDs PUD

- Co – therapy with PPI
  - Used at standard dose
  - H_2RA not recommended (for dyspepsia)
- Co – therapy with misoprostol
  - Lower dose of 600μg/day
  - Limited by abdominal cramping, diarrhea
- Use of COX – 2 inhibitor: Controversial

COX – 2 Inhibitors & CVS Toxicity

- Risk ↑ with:
  - ↑ COX – 2 selectivity e.g. celecoxib
  - Higher dosages
  - Longer duration of treatment
  - Pre – existing cardiovascular risk.
- Naproxen is the preferred NSAID with the least CVS risk
- Consider:
  - Acetaminophen
  - Tramadol, narcotics

NSAID Selectivity	Drugs	Notes
COX-2 Selective	Celecoxib	• Increased risk for CV events • Decreased risk for GI side effects
Semiselective	Diclofenac Etodolac Indomethacin Meloxicam Nabumetone Piroxicam Sulindac	• Increased affinity for COX-2 but still retain activity for COX-1 • Use with caution in patients at increased CV risk • Diclofenac has demonstrated the highest CV risk of any of the nonselective NSAIDs
Nonselective	Ibuprofen Naproxen	• Decreased risk for CV events • Increased risk for GI side effects • Naproxen has demonstrated the least CV risk compared to others
Irreversible Nonselective	Aspirin	• Cardioprotective at low doses • Increased risk for GI side effects

Other adverse effects of NSAIDs

- Interstitial nephritis
- Challenges when managing HTN

GERD

Goal Of Therapy

- Alleviate symptoms
- Promote esophageal healing
- Prevent recurrence
- Avoid long term complications: **Barrett esophagus**

Antacids

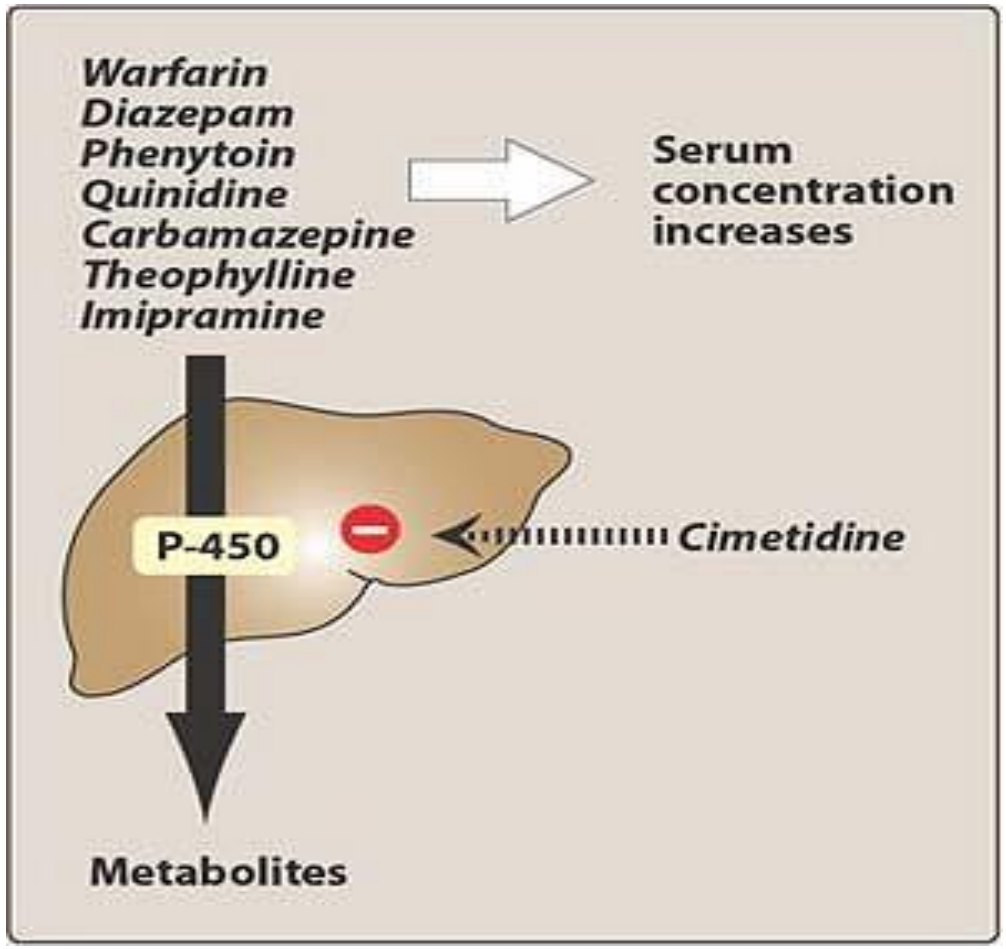
- Used for mild GERD
- Relieve symptoms rapidly (minutes)
- Duration of action:
  - 30 minutes on an empty stomach
  - Hours if taken 1 hr. after meals
- Requires frequent dosing

Antacids

- Addition of **alginic acid** (improve symptom relief)
- No healing of erosive esophagitis.
- Electrolyte abnormalities (especially in renal disease)
- Diarrhea, constipation

H_2RAs

- Used for mild – moderate GERD
- Symptom relief (30 minutes)
- Duration of action (10 hours)
- Prophylaxis for postprandial GERD
- Reduces nocturnal acid secretion.
- **Tachyphylaxis** occurs with continued use
- Cimetidine is CYP450 inhibitor



PPIs

- Drug of choice for frequent, moderate – severe GERD
- Symptom relief within 2 to 3 hours
- Longer duration of action (24 hours)
- Superior
- Improvement in physical functioning & sleep

Prokinetic Agents

- Metoclopramide and bethanechol
  - ↑ LES pressure
  - Stimulate upper GIT motility
- Symptomatic relief
- Numerous side effects
  - Sedation, Anxiety
  - Extrapyramidal symptoms
- Used:
  - GERD refractory to other treatment
  - Delayed gastric emptying.

Sucralfate

- No effect on intragastric pH
- Requires multiple daily dosing
- A/E:
  - Binding of other drugs
  - Aluminium toxicity (renal failure).
  - Constipation, electrolyte imbalances.
  - Requires pH ≤4 for conversion to active form
    - Reduced effectiveness if combined

Maintenance Therapy

- Keep patient symptom free
- Daily PPI is more effective

Severity of GERD	Medical Management
Stage I Sporadic uncomplicated heartburn, often in setting of known precipitating factor. Often not the chief complaint. Less than 2-3 episodes per week. No additional symptoms.	Lifestyle modification, including diet, positional changes, weight loss, *etc.* Antacids and/or histamine H_2 receptor antagonists as needed.
Stage II Frequent symptoms, with or without esophagitis. Greater than 2-3 episodes per week.	Proton pump inhibitors more effective than histamine H_2 receptor antagonists.
Stage III Chronic, unrelenting symptoms; immediate relapse off therapy. Esophageal complications (*e.g.*, stricture, Barrett's metaplasia).	Proton pump inhibitor either once or twice daily.

3. DRUG TREATMENT OF PORTAL HTN & UPPER GI BLEEDING (UGIB)

5/2/2019

UGIB

- Common medical emergency
- Categorized as:
  - Variceal
  - Non variceal
- 70% of the time, UGIB is from **duodenal or gastric ulceration & erosion.**
- **Esophageal varices & portal HTN with gastropathy** account for 15%.
- Other causes account for 10 – 15%.

History & exam

- Hematemesis: whenever you see a patient with hematemesis **always consider that the bleed may be due to epistaxis.**
- Melena: Do a DRE & check for tarry black stool on the examining finger.
- H/O NSAID, antiplatelet & anticoagulant use e.g. warfarin
- Do an NG aspirate

Diagnosis

- Upper GIT Endoscopy (OGD)
- Angiography
  - Diffuse blush of extravasating contrast
  - Detectable: 5ml/ minute
  - Super – selective catheter: 1ml/min

Localizing an acute bleed by angiography

- Inject **vasopressin** – 0.2 units/ minute through the catheter over 20 – 40 minutes: this reduces splanchnic blood flow
- May need to increase duration of infusion in elderly due to atherosclerotic vessels
- **Epinephrine** 8 – 30 mcg/ minute for vasoconstriction

Non – variceal bleeding

- PUD
- Stress related mucosal bleeding (SRMB): usually in the upper stomach in critically ill patients.
- Erosive esophagitis
- Mallory Weiss tear: due to retching and vomiting usually in a young alcoholic male

Cont.

- Malignancy: esophageal carcinoma
- Vascular anomalies
- Acute pancreatitis
- Bleeding disorders

Treatment

- Hemodynamic instability:
  - IV access with two large – bore catheters
  - IV fluid repletion – crystalloids, colloids, blood
- **Endoscopic hemostasis is the cornerstone**

PUD Bleed

- Treatment with anti – secretory drug after endoscopy (promote healing of ulcer)
  - H_2RAs are not recommended
  - PPIs are drugs of choice (IV infusion for 72 hours then oral)
- Somatostatin or octreotide is not recommended

Stress Related Mucosal Bleed

- Stress ulcers may be single or multiple; superficial gastric, duodenal or gastroduodenal in critically ill patients.
- Can cause profuse bleeding.
- Common in: burns, head injury, acute liver failure, ARF, gram –ve sepsis, prolonged mechanical ventilation, DIC

Cont.

- Inhibition of gastric acids is the primary target (pH ≥4)
- H_2RAs most widely used: Continuous or intermittent infusion
- IV PPIs can also be used
- Prophylaxis: sucralfate

Mallory Weiss Tear

- Seen in alcoholics
- Common in young males
- Pathophysiology: severe retching & vomiting
- Management: endoscopy & band ligation; local epinephrine; thermocoagulation

UGIB in the immunocompromised patients

- CMV: ganciclovir
- HSV: acyclovir, valacyclovir
- Fungal: candida, aspergillosis, mucor

GIT bleeding in hepatic encephalopathy

- Use laxatives if melena stool is present: **lactulose**
- Lactulose (15 – 30mL 8hrly) is a disaccharide which is taken orally and reaches the colon intact, to be metabolized by colonic bacteria.
- The dose is increased gradually until the bowels are moving twice daily.

What is the MoA of lactulose in hepatic encephalopathy?

- ↓ pH of colonic content hence:
  - ↓ breakdown of nitrogen – containing compounds to ammonia & other potential cerebral toxins
  - Limiting colonic ammonia absorption
- Osmotic laxative effect
- Promotes incorporation of nitrogen into bacteria

Variceal Bleed

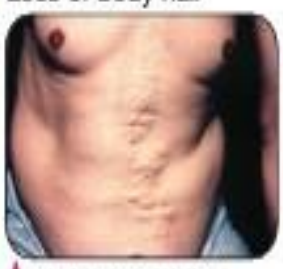
Etiology

- Varices are dilated sub – mucosal veins in the esophagus or stomach caused by **portal hypertension.**
- They are a cause of ~80% of UGIB in chronic liver disease
- Diagnosis: OGD
- Re – bleeding occurs in 30 – 40%
- Mortality occurs in 40%

Risk factors for bleeding from varices

- Size of varices
- Severity of liver disease
- Continued alcohol intake
- On UGI endoscopy: wale markings, hematocystic/ red spots on varix

Chest
Loss of body hair



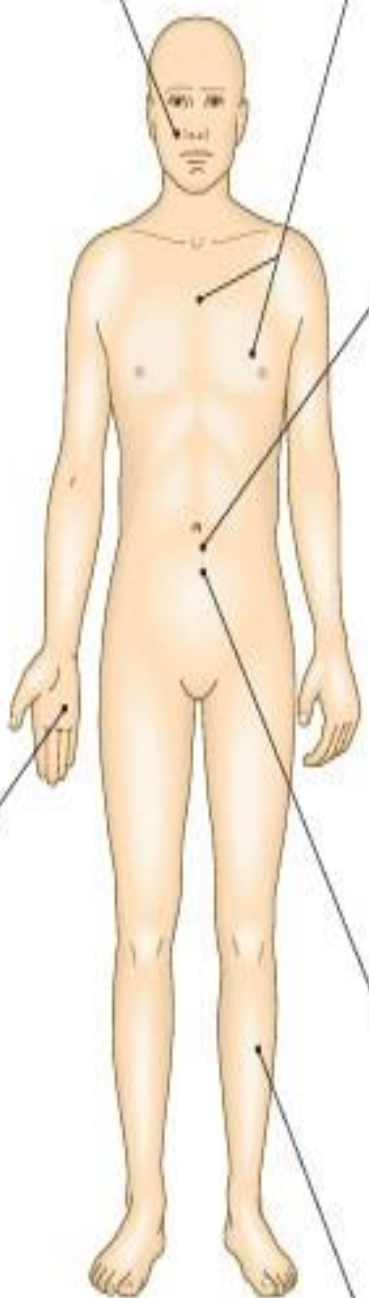
Gynaecomastia

Spider naevi

Face 2
Jaundice
Spider naevi
Parotid swelling

Xanthelasma and jaundiced sclera in a patient with chronic cholestasis

Kayser–Fleischer rings in Wilson's disease



Abdomen: inspection 4
Scars
Distension
Veins
Testicular atrophy

Aspiration of ascitic fluid

Dilated abdominal wall veins (caput medusae)

Hands 1
Clubbing
Dupuytren's contracture
Leuconychia
Bruising
Flapping tremor (hepatic encephalopathy)

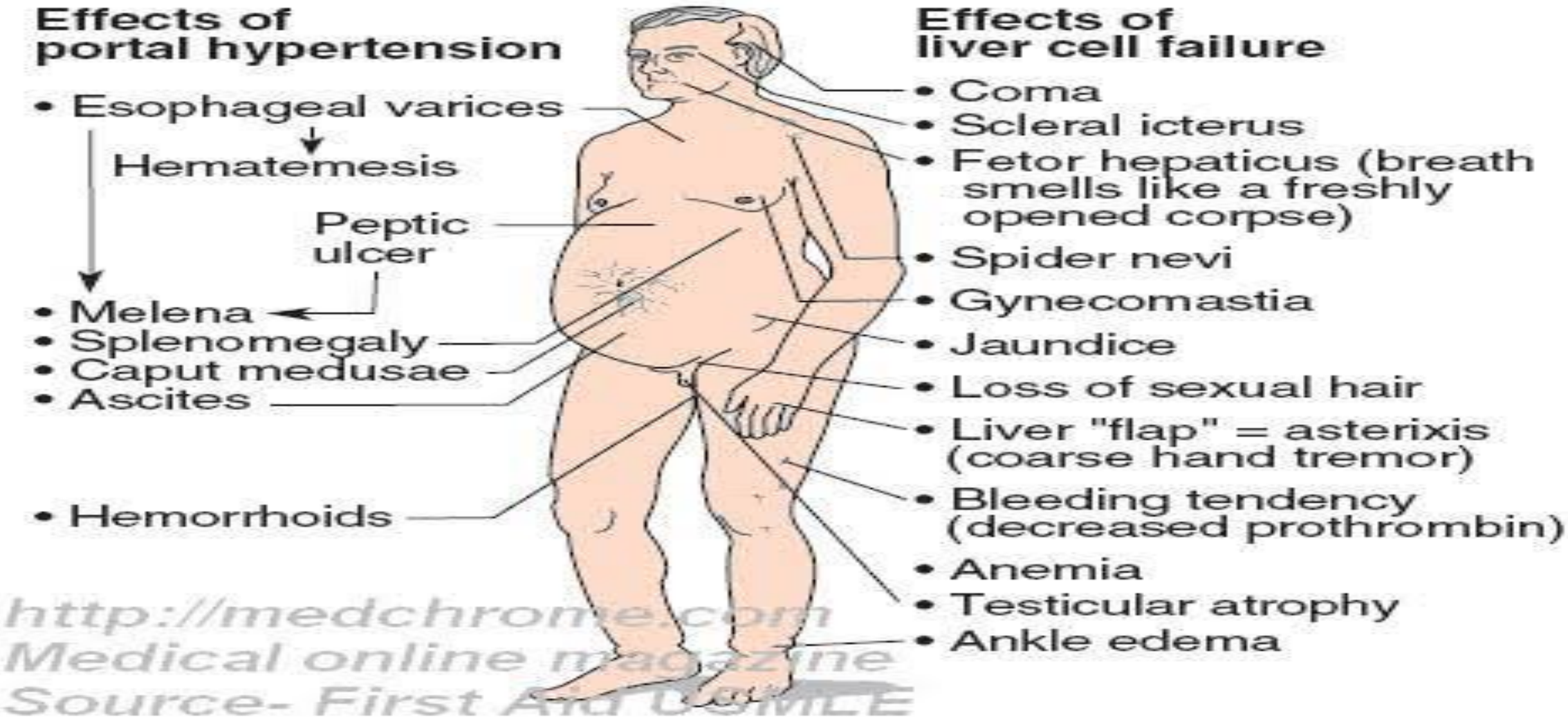
Palmar erythema

Abdomen: palpation/percussion/auscultation 5
Hepatomegaly
Splenomegaly
Ascites
Palpable gallbladder
Hepatic bruit (rare)
Tumour

Observation

- Unkempt
- Smell of alcohol or fetor hepaticus
- Encephalopathy
- Weight loss
- Scratch marks from itching

Legs 6
Bruising
Oedema



http://medchrome.com
Medical online magazine
Source- First Aid USMLE

Presentation of cirrhosis/portal hypertension.

Cont.

- On examination of a patient with UGIB, ensure the stigmata of chronic liver disease (CLD) are assessed.
- Auscultate for a venous hum in splenomegaly.

Goals

- Medical emergency
- Treatment goals:
  - Volume resuscitation
  - Acute treatment of bleeding
  - Prevention of recurrence

Pharmacologic Interventions

- **Vasopressin**: 0.4 units/ minute
- **Terlipressin**: 2mg 4 – 8hrly then half dose for 5 – 7 days
- **Somatostatin**: 250 μg IV bolus; repeat every 3hrs. Followed by 250 μg/hr for 5 – 7 days.
- **Octreotide** (longer half life): 50 – 100 μg IV bolus followed by 25 – 50 μg infusion/ hr.
- Above interventions alone do not influence mortality.
- It is advisable to follow up with endoscopy.
- To prevent recurrence, use a **beta adrenoceptor blocker e.g. propranolol.**

Terlipressin

- Synthetic analogue of vasopressin
- Fewer side effects
- Improve patient survival.

Vasopressin

- Terminating bleeding in 60%; esp. in bleeding involving small vessels and capillaries as seen in mucosal tears & stress ulcers.
- Large ulcers may require embolization.
- Concerns:
  - HTN (water retention); Angina; abdominal cramps; diarrhea; cardiotoxicity (MI, arrhythmias); Tissue necrosis on extravasation
- Continuous IV infusion (short half life)
- Concurrent Nitroglycerin (NTG) 10 – 30 μg/min minimizes the side effects

Octreotide

- Synthetic analog of somatostatin
- Longer half life
- Given as bolus then followed by infusion
- Well tolerated
- First line treatment

Infection Prophylaxis: Short term antibiotics

- Variceal haemorrhage: risk factor for severe bacterial infections (SBP)
- 7 days of antibiotic prophylaxis:
  - PO Norfloxacin (400 mg BID)
  - IV/PO Ciprofloxacin (400 mg BID)
  - IV Ceftriaxone (1 g/day)

β - Blockers

- Primary & secondary prophylaxis
- Non – selective β – adrenergic blockers: ↓ portal pressure:
  - ↓ in cardiac output (β1)
  - ↓ in splanchnic flow (β2)
  - Propranolol, nadolol
- First line therapy: propranolol 20mg BD (prevents recurrence)
  - Also sorbitrate 5 – 10mg TDS
- Indefinite treatment

Vessel embolization

- MC through a catheter at the site of bleeding
  - Coils
  - Glue
- Also:
  - Gelatin
  - Fiber

Endoscopy

- Injection scleropathy
- Sangstaken – blackmore tube (24 – 48 hrs.)
- PPI arrests bleeding in ulceration

Summary of principles of management of UGIB

- IV crystalloids/ colloids: to replenish volume (consider inserting a CV catheter)
- NG tube for gastric lavage with ice saline or cold tap water
- Prokinetics: IV metoclopramide or erythromycin
- Transfusion: packed cells/ FFP
  - FFP is used in patients with CLD; target INR 1.4 – 1.6
  - Cryoprecipitate is used if there's advanced disease with low fibrinogen levels

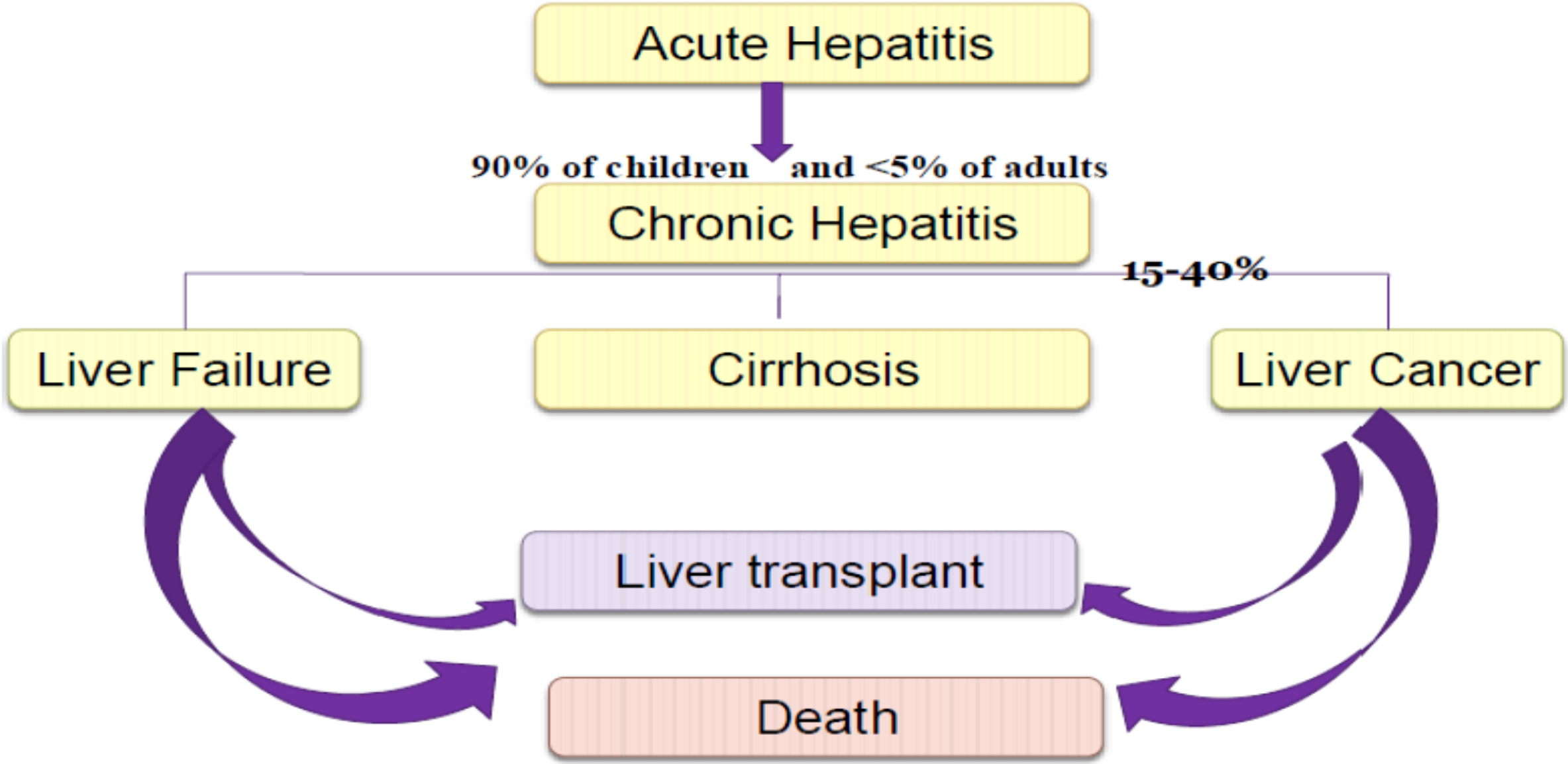
Cont.

- Consider platelet infusion if aspirin – associated bleeding
- IV desmopressin if in renal failure
- Antibiotics – ceftriaxone/ FQ
- Endoscopy: Find out the cause & treat it.

4. MANAGEMENT OF CHRONIC LIVER DISEASE 22/03/2019

BY: DR. KUBO

Disease progression



1. Diagnostic criteria of Chronic Hepatitis B

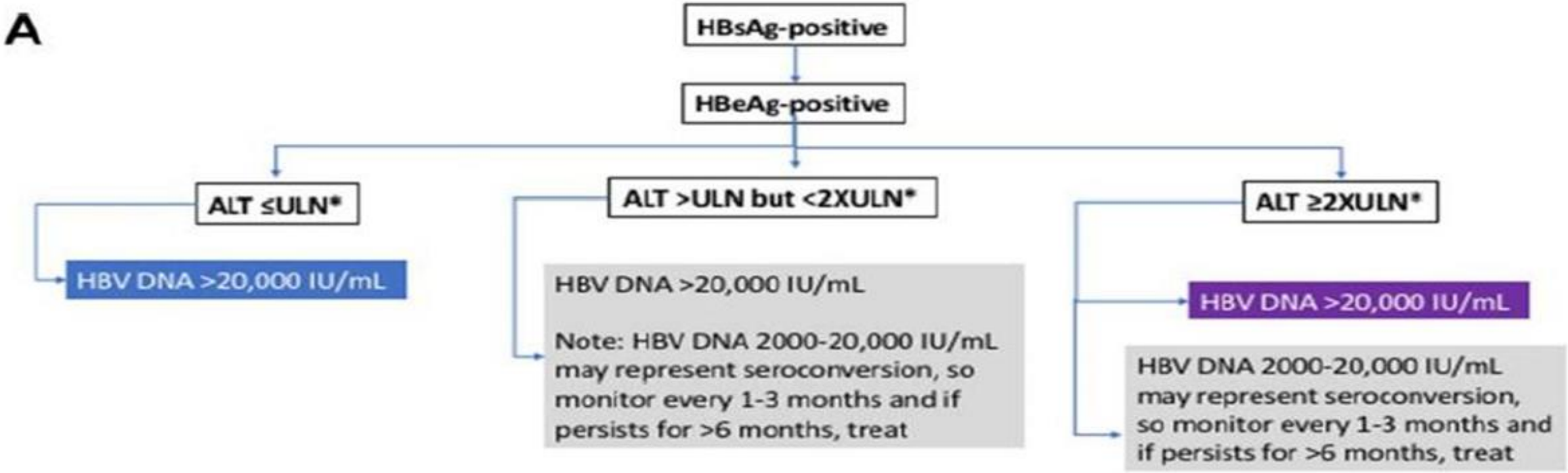
- ***HBsAg*** +ve for ≥ 6 months.
- Serum ***HBV DNA*** varies from undetectable to several billion IU/mL. Subdivided into HbeAg +ve & -ve:
  1. HBeAg +ve CHB: HBV DNA levels are typically > 20, 000 IU/mL.
  2. HBeAg -ve CHB: HBV DNA levels have lower values (2000 – 20000 IU/ml).
- Normal or elevated ***ALT &/or AST levels***.
- ***Liver biopsy*** results show **chronic hepatitis** with variable **necroinflammation** &/or **fibrosis**.

Goals of treatment

1. Suppression of HBV replication to undetectable levels.
2. Decrease hepatic necroinflammation & fibrosis.
3. Prevent progression to cirrhosis, liver failure & HCC.

Whom to treat: Depends!

A



Recommendations:

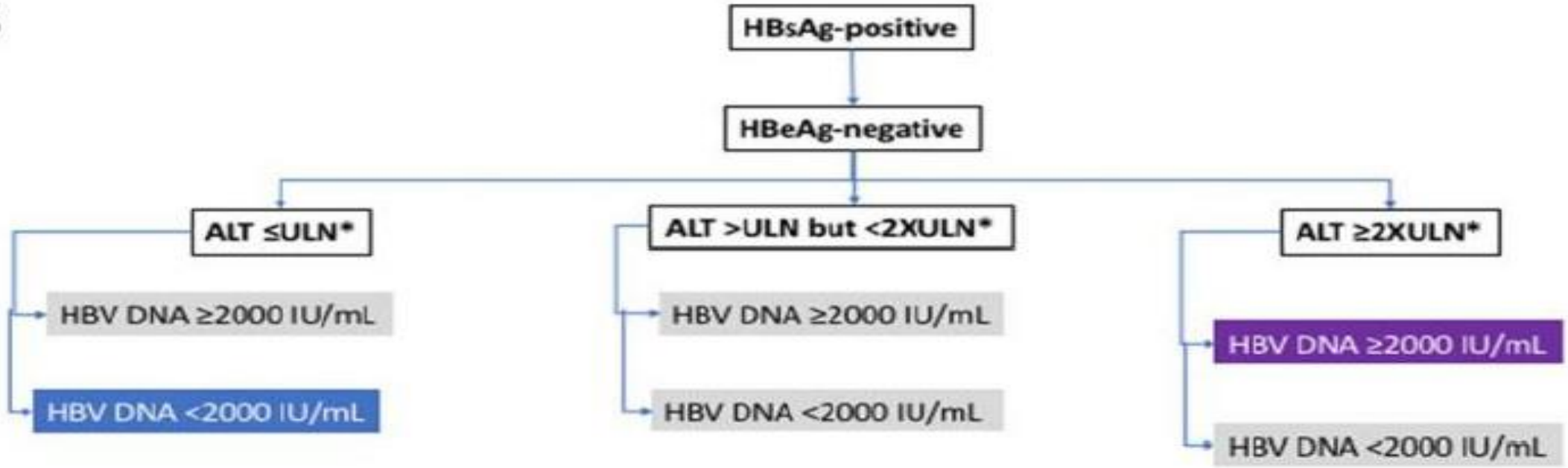
Treat

Do not treat. Monitor with ALT and HBV DNA levels every 3-6 months and HBeAg every 6-12 months.

Exclude other causes of ALT elevation and assess disease severity with non-invasive tests and/or liver biopsy. If staging indicates ≥F2 or ≥A3, treat. If other causes of ALT >ULN excluded and elevation persists, treat, especially if age >40.

If HBeAg Negative

B



Recommendations:

Treat

Do not treat. Monitor with ALT and HBV DNA levels every 3-6 months and HBsAg annually.

If ALT ≤ULN, monitor ALT and HBV DNA every 3 months for 1 year, then every 6 months.
If ALT elevated, exclude other causes of ALT elevation and assess disease severity with non-invasive tests and/or liver biopsy. If staging indicates ≥F2 or ≥A3, treat. If persistent ALT >ULN with HBV DNA ≥2000 IU/mL, treat, especially if age >40.

What to Use?

Injectables in HBV treatment

- Immunomodulators

Interferon alpha 2b

IFN

Peg- interferon alpha 2a/2b

PEG IFN

Mode of action

- Enhances phagocytic activity of macrophages.
- Inhibits viral replication in virus – infected cells.
- Increases cytotoxicity of lymphocytes for target cells.

a. PEGylated IFN

- Addition of ***poly-ethylene glycol (PEG)*** to standard IFN has several benefits:
  - Shields IFN from enzymatic degradation thus ***lowers systemic clearance***.
  - Allows ***less frequent dosing*** – once a week SC
  - Achieves ***higher & more sustained IFN serum concentrations .***

Oral drugs: nucleoside/ nucleotide analogues

- ***L***amivudine (3TC/LAM)
- ***A***defovir
- ***T***enofovir (TDF): usually combined with **lamivudine**
- ***T***elbivudine
- ***E***ntecavir
- ***E***mtricitabine (FTC)

MoA of nucleoside/ nucleotide analogues

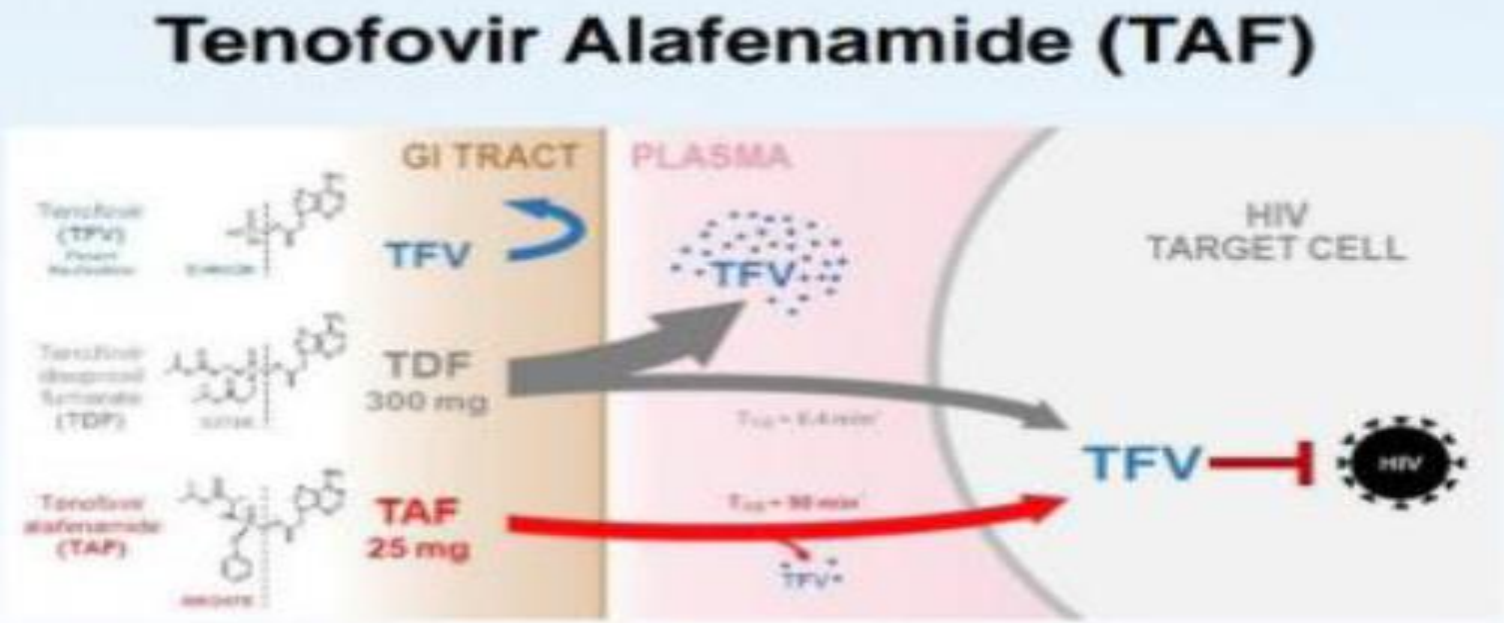
- They mainly act by ***inhibition of HBV DNA polymerase enzyme*** activity resulting in a ***reduction of viral replication***.

Antiviral agent	Potency against HBV	Resistance barrier	Activity against HIV	Cost
Interferons	Moderate	Not applicable	Moderate	High
Tenofovir	High	High	High	Low (high in Hong Kong and other Asian countries)
Entecavir	High	High	Weak	High
Emtricitabine	Moderate	Low	High	Low
Telbivudine	High	Low	Unclear	High
Lamivudine	Moderate–high	Low	High	Low
Adefovir	Low	Moderate	None (at 10 mg dose)	High

Preferred agents (AASLD 2018 guidelines)
American Association for the Study of Liver Diseases

DRUG	ADVERSE EFFECTS
PEG IFN α2a (adults)	Flu – like symptoms, fatigue, cytopenia, autoimmune disorders (RA, SLE)
Standard IFN α2b (children)	Anorexia, weight loss
Tenofovir Disoproxil Fumarate (TDF)	Nephropathy, Fanconi Syndrome, Osteomalacia, Lactic acidosis
Tenofovir Alafenamide (TAF)	Lactic acidosis
Entecavir	Lactic acidosis

TDF Vs. TAF



- 91% lower plasma TFV levels minimize renal and bone effects while maintaining high potency for suppressing HIV
- less effect on renal tubular and overall proteinuria and eGFR than TDF
- little to no effect on bone density

Lee W, *AAC*, 2005; Birkus G, *AAC*, 2007; Babusis D, *Mol Phar*, 2013; Ruane P, *JAIDS*, 2013; Sax P, *JAIDS*, 2014; Sax P, *Lancet*, 2015

ACTHIV
THE AMERICAN CONFERENCE FOR THE TREATMENT OF HIV

Non – preferred
AASLD 2018 Guidelines

DRUG	ADVERSE EFFECTS
Lamivudine	Pancreatitis
Adefovir	ARF, Fanconi Syndrome, Lactic Acidosis
Telbivudine	Creatinine kinase elevation, myopathy, peripheral neuropathy, lactic acidosis

Advantages of PEG IFN

- Finite duration (24 wks. up to a year).
- Absence of resistance.
- Higher rates of anti – Hbe & anti – HBs seroconversion with 12 months of therapy.

Disadvantages of PEG IFN

- Moderate antiviral effect
- Inferior tolerability
- Risk of adverse events
- Subcutaneous injections

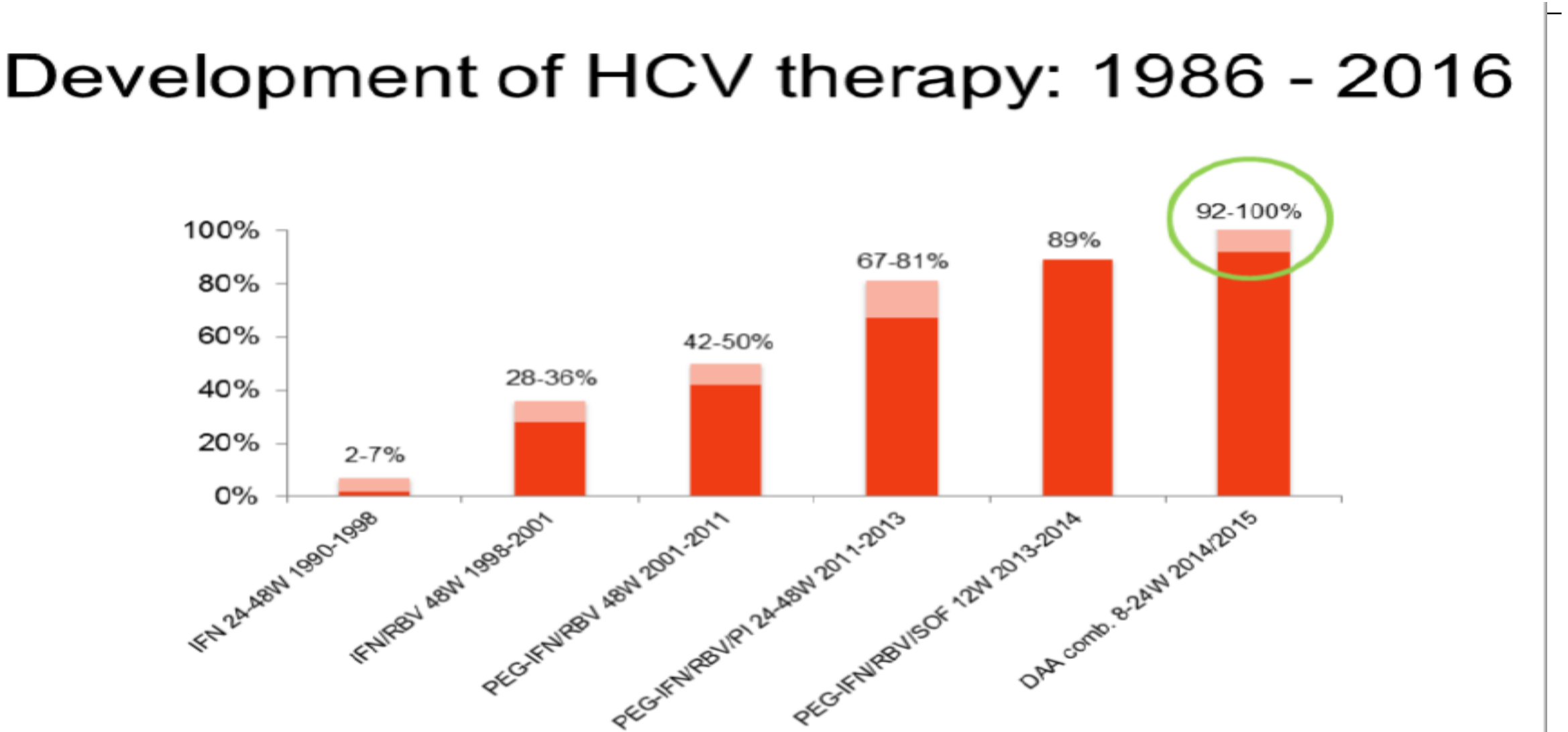
Advantages of Nucleos(t)ide analogues

- Potent antiviral effect
- Good tolerance
- Oral administration

Disadvantages of Nucleos(t)ide analogues

- Infinite duration
- Risk of resistance
- Unknown long term safety

2. Current Management of Hepatitis C



Goal of treatment

- The goal of Rx of HCV – infected persons is to ***reduce all – cause mortality*** & liver – related health adverse consequences, including ***end – stage liver disease*** & ***HCC***, by the achievement of ***virologic cure*** as evidence by an SVR.

HCV replication & drug targets

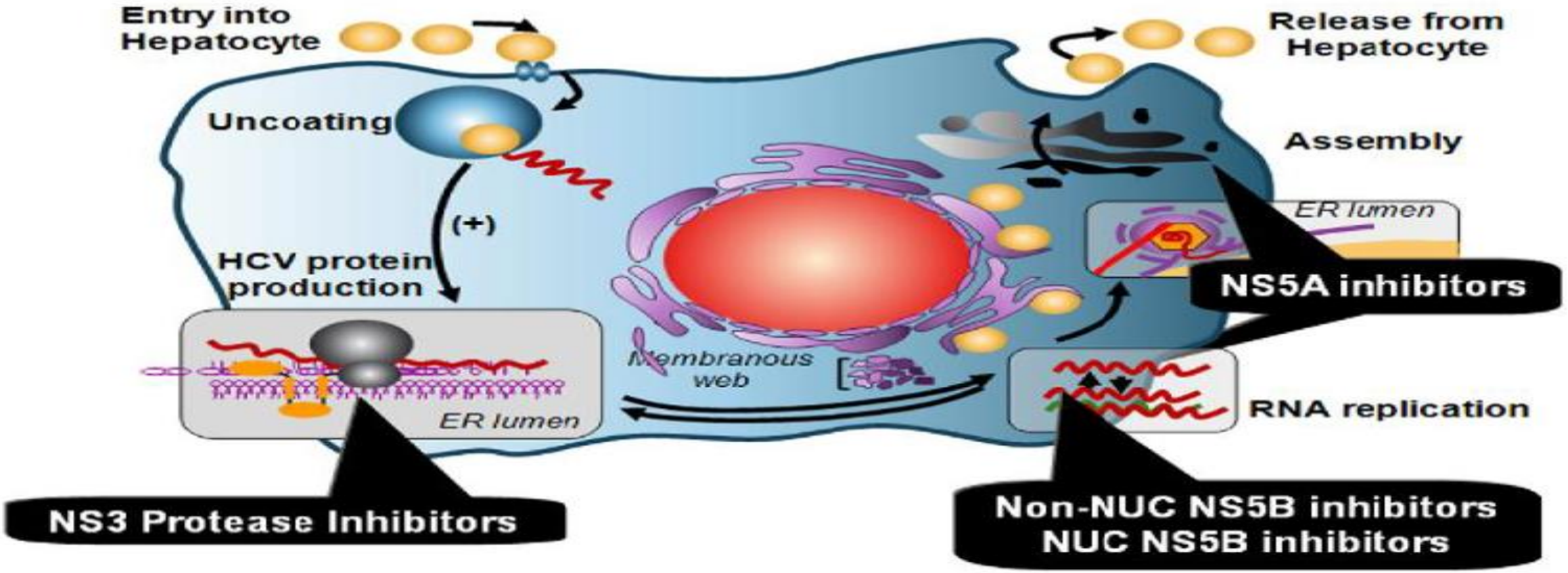
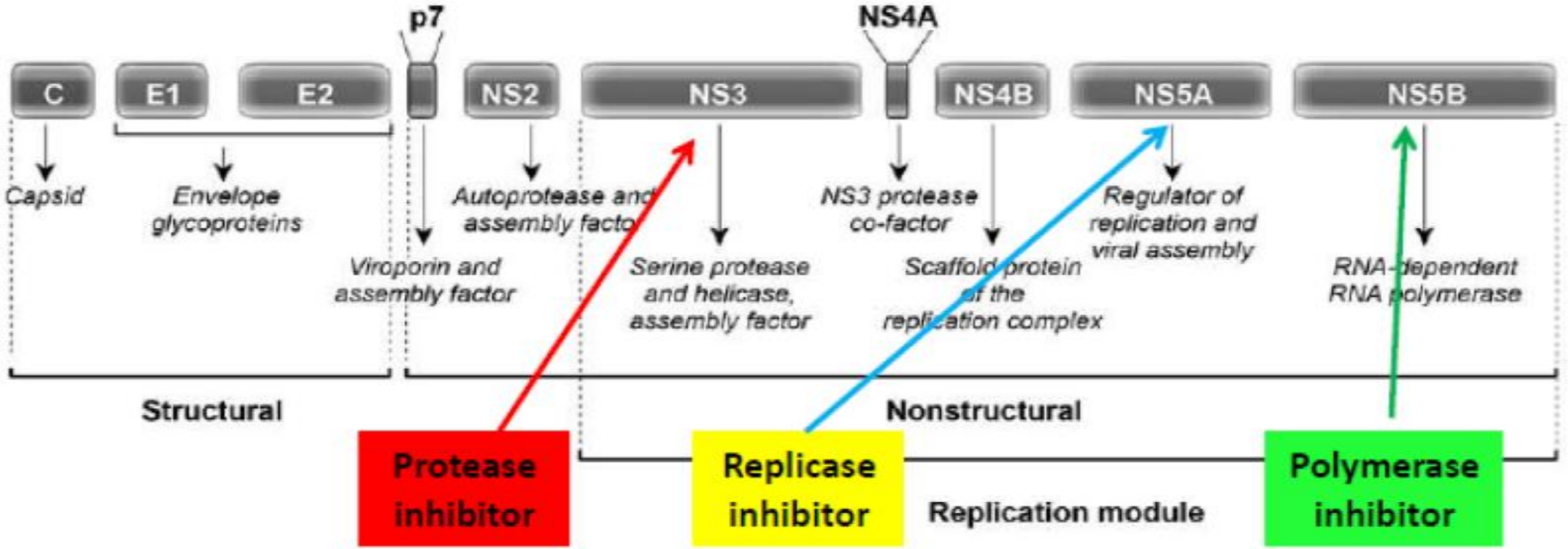
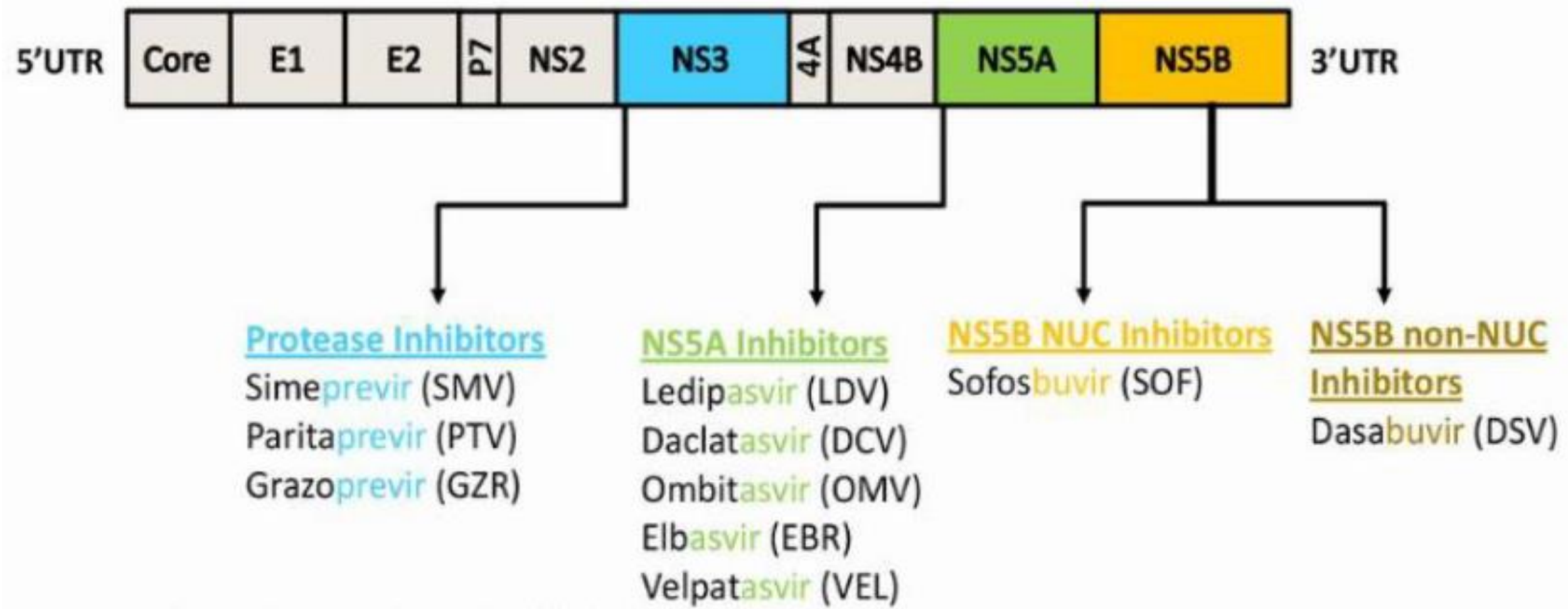


Figure 1: Specific targets of the direct acting antiviral agents.

HCV structural & non – structural proteins



Approved HCV – Directing Acting Antiviral (DAA) Agents



Bertino G. *World Journal of Hepatology*. 2016;8(2):92-106.

Cure rates can be optimized by:

- Combining drugs with synergistic antiviral effects.
- Modifying treatment duration.

Sofosbuvir (*Sovaldi*)

- NS5B NUC Inhibitors
- MoA: HCV polymerase inhibitor.
- This is indicated for the Rx of HCV infection as a component of a combinational DAA regimen for patients with ***HCV mono – infection*** & ***HCV – HIV 1 coinfection***.

Cont.

- Advantages that make Sofosbuvir the ideal candidate to becoming the backbone for several IFN – free regimens:
  - Low toxicity
  - High genetic barrier to resistance
  - Minimal drug interactions with other DAAs

3. Management of liver cirrhosis

- Functions of the liver:
  - Detoxification
  - Gluconeogenesis
  - Protein synthesis
  - Coagulation etc.

Cont.

- Cirrhosis is the fibrosis and conversion of the normal hepatic architecture into structurally ***abnormal nodules***.
- Histologically, it is characterized by destruction of hepatocytes & their replacement by fibrous tissue.
- There is a resultant reduction in the liver span below 8 – 12cm.

Pathophysiologic outcomes of cirrhosis

a) Hepatic encephalopathy
b) Ascites (& edema): due to hypoalbuminemia
   - Spontaneous bacterial peritonitis
   - Pleural effusion
c) Portal HTN & esophageal varices
d) Coagulation disorders

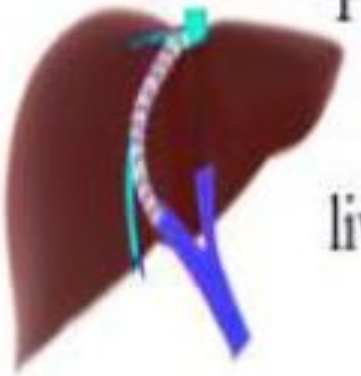
a. Management of hepatic encephalopathy

- This is the ***reversible impairment of neuropsychiatric abilities associated with impaired hepatic function***.
- It is due to ***accumulation of gut derived nitrogenous substances*** in the systemic circulation.

Hepatic Encephalopathy (HE)

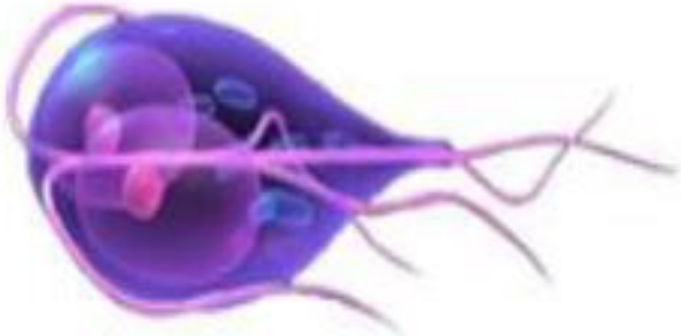
Diseased Liver

Failure to Metabolize NH_3



Portosystemic Shunt (Blood bypasses liver, reaches general circulation)

Toxins Affect the Brain (HE)



Gut Flora

Ammonia (NH_3), Glutamine
Methionine, Nitrogen,
Serotonin, GABA

Management approach

- Reduce production of blood ammonia:
  - Limit dietary protein intake; diet should be of high CHO, low salt & moderate protein.
  - Enhance removal of nitrogenous compounds: use of ***lactulose 30 – 45 ml TID*** which is an osmotic laxative
    - A/E: flatulence, diarrhea, abdominal cramps

Role of antibiotics

- For ↓ ***of intraluminal urease – producing bacteria*** that may lead to excess ammonia production. The following are used:
  1. Neomycin
  2. Rifaximin
  3. Metronidazole

DRUG	NOTES	ADVERSE EFFECTS
Neomycin	• Aminoglycoside AB • Poorly absorbed from the gut.	Rare: nephrotoxicity & ototoxicity
Rifaximin	• Derivative of rifampin. • Inhibits bacterial protein synthesis • Absorption < 0.5% • Reduced risk of CYP450 mediated drug interactions.	Flatulence, constipation
Metronidazole	• Undergoes reduction within anaerobic bacteria with accumulation of toxic products	Peripheral neuropathy, nausea, metallic taste, Disulfiram like effect

b. Management of ascites

- Fluid restriction
- Sodium restriction < 2g day
- Avoid NSAIDs: cause sodium retention
- Oral diuretics
  - Starting doses: spironolactone 100mg/ furosemide 40mg single morning dose
  - Increase every 3 to 5 days; max dose is 400/160mg

DRUG	NOTES	ADVERSE EFFECTS
Furosemide	• Inhibits the $Na^+/2K^+/2Cl$ transporter in the loop of Henle.	Ototoxicity, hypovolemia, hyperuricemia, hypomagnesemia & K^+ wasting.
Spironolcatione	• Aldosterone antagonism in the collecting tubules..	Hyperkalemia & gynecomastia

c. Management of Spontaneous Bacterial Peritonitis (SBP)

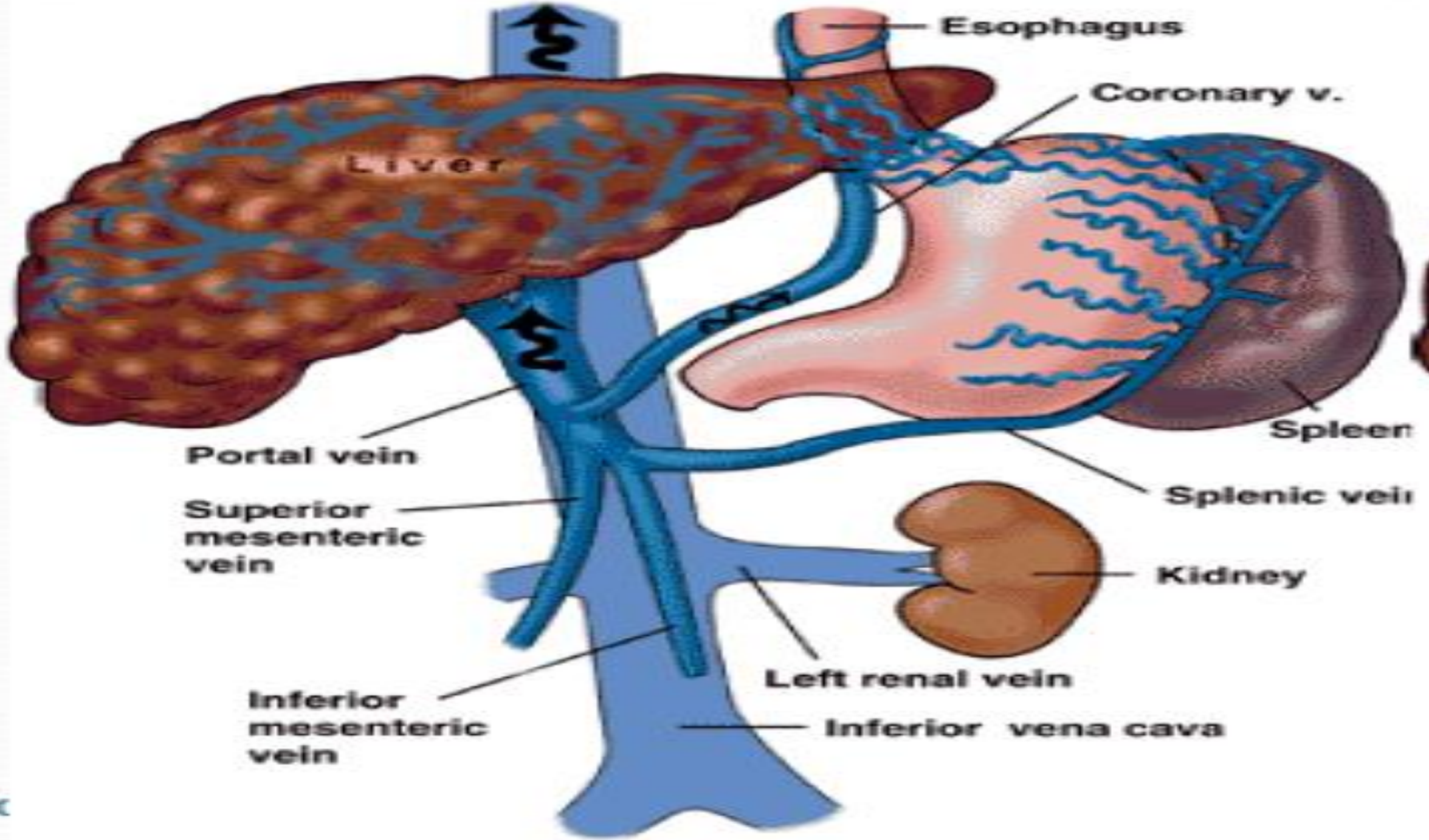
- Bacterial infection of ***pre – existing ascetic fluid*** without evidence of an intra – abdominal source.
- Usually caused by gram negative organisms:
  - ***E. coli***
  - ***Klebsiella pneumoniae***

Treatment

- 3rd generation cephalosporins:
  - Ceftriaxone 2g/d
  - Cefotaxime 2g TID
  - Fluoroquinolones: ciprofloxacin, levofloxacin
- Duration of Rx: 5 – 10 days

d. Esophageal varices & portal HTN

- Approach
  - Primary prophylaxis to prevent bleeding
  - Management of variceal hemorrhage
  - Secondary prophylaxis to prevent bleeding in those who have had a previous bleed


Esophagus
Coronary v.
Liver
Portal vein
Superior mesenteric vein
Splenic vei
Kidney
Left renal vein
Inferior mesenteric vein
Inferior vena cava

Emergency management

- Replenish circulating volume: IVFs, colloids, blood transfusion
- Vasoactive therapy to decrease portal blood flow:
  - ***Somatostatin analogue e.g. IV octreotide 50 – 100µg bolus;*** continue with ***IV infusion of 25 – 50 µg/ hr.*** → results in splanchnic bed vasoconstriction.
  - ***Vasopressin analogues e.g. Terlipressin***
    - *It isn't selective for splanchnic vessels can cause coronary VC & hence angina pains*)

Definitive management

- Endoscopic band ligation
- Endoscopic injection sclerotherapy: injection of sclerosants
  - Ethanolamine
  - Sodium tetradecyl sulfate
  - Polidocanol
  - Sodium morrhuate

Bleeding prophylaxis

- This is achieved by the use of ***β – blockers*** to decrease blood flow to mesenteric vessels (negative inotropy results in reduction in cardiac output)
- The following can be used:
  - Propranolol 20mg TID
  - Carvedilol 6.25 mg
  - Nadolol 20mg
- The dose is titrated to achieve a HR of 55 – 60 bpm (or 25% lower than the baseline HR)
- A/E: bronchospasm, glucose intolerance

e. Coagulation defects

- Due to reduced synthesis of coagulation factors
- Management is initiated if INR > 1.5 using:
  - FFP
  - Vitamin K

5. PARENTERAL NUTRITION

BY: DR. KUBO

8. CHEMOTHERAPEUTICS
LEVEL VI MBCHB
2019

COMPILED BY NAILA KAMADI

OUTLINE

Cancer chemotherapeutic agents

Principles of cancer chemotherapy

CANCER CHEMOTHERAPEUTICS AGENTS

BY: DR. M. EZZI

TYPED BY NAILA KAMADI

Chemotherapy

- These include drugs that treat cancer cells.
- Cytotoxic therapy is directed toward ***rapidly dividing cells***.

General classification of cancer chemotherapeutic agents

1. ***Conventional chemotherapeutic drugs***: these tend to act on the cell cycle hence affecting the DNA e.g. alkylating agents, anti – metabolites
2. ***Targeted therapies***: act at a particular antigen that the cancer cells are expressing e.g. Rituximab (act on CD20 expressing cell by antibody or cell mediated cytotoxicity.
3. ***Small molecule/ tyrosine kinase inhibitors:*** act on tyrosine kinase (2nd messenger pathways e.g. CAMP pathway) preventing phosphorylation & further down – stream signaling.
4. ***Immuno – therapy:*** these are drugs that activate the immune system to kill the cancer cells.

Mechanism of Action

- Chemotherapy:
  - Damage DNA
  - Interfere with DNA synthesis
  - Inhibit cell division
- Classified by their effect on cell cycle
  1. Phase specific agents (schedule dependent)
  2. Phase non – specific agents (dose dependent)

The cell cycle

- Stages that a cell undergoes before cell division.
- Mitosis: G1 – M phase
  - ***G1 (Gap) phase***: cell is resting & accumulating the nutrition for the cell to undergo the S (synthetic) phase
  - ***S phase***: cell starts to synthesize new DNA material for mitosis.
  - ***G2 (Gap) phase***: cell ensures the DNA is free of mutations, insertions, deletions, translocations etc.; incase the errors are present repair or cell death happens.
  - ***M (mitotic) phase***: actual cell division takes plase.

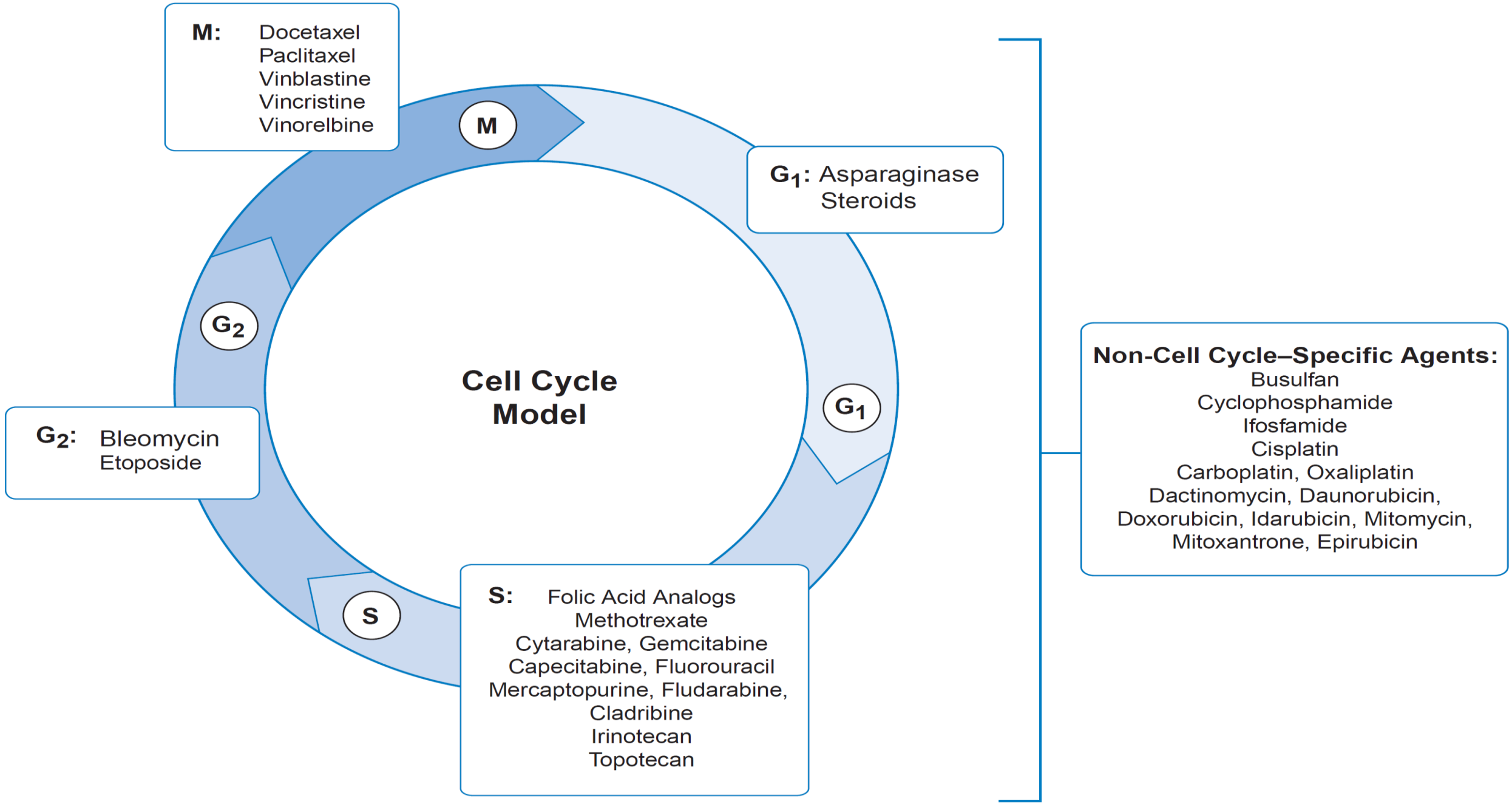


FIGURE 89-2 Cell cycle and effects of representative cytotoxic drugs on phases of the cell cycle.

Factors Influencing Chemotherapy Response

- Growth fraction: this represents the speed of division of tumor cells; slow growing tumors tend to be more chemo – resistance.
  - The objective of successive chemotherapy cycles is ***further decrease in size of tumor mass.***
- Dose intensity
- Dose schedule
- Drug resistance
- Tumor site: presence of physiological barriers & privileged tumor sites.
- Patient's performance status.

a. Dose Intensity

- This is the chemotherapy ***dose per unit time (mg/m^2/week)***
- Drug resistance can be overcome by ***escalating dose intensity*** as follows:
  - Increasing dose per cycle
  - Shortening interval between cycles, i.e., ***dose dense treatment***
- Increasing the dose intensity is limited by ***major dose related toxicity*** in the normal, rapidly dividing cells in the body e.g. mucosal cells, bone marrow.

b. Schedule Dependency

- Chemotherapy drugs are given in cycles, with in – between recovery periods depending on:
  - Type of cancer
  - Drugs used
- This is an important determinant of response/ efficacy:
  - Affects toxicities
  - Pharmacokinetics of drug

Combination Chemotherapy

- Most chemotherapeutic drugs are given as combinational agents since most tumors show ***partial, short response to single – agent therapy***.
- Combination therapy offers a broader coverage against resistant cell lines.
- Principles:
  - Different mechanisms of action e.g. alkylating agent with antimetabolite; mitotic spindle poison with alkylating agent.
  - No overlapping toxicities
  - Used in optimal dose & schedule to have the most benefit.
  - Agents with demonstrable activity

Cont.

- ***Primary chemotherapy***: 1st line treatment administered to a cancer patient.
- ***2nd line/ salvage chemotherapy***: given after a tumor progresses on the 1st line chemotherapy, i.e., tumor is refractory to primary therapy.
  - Aim: to allow the patient to be symptom free as response is not as good with the 1st line therapy.
- ***Consolidation***: Additional chemotherapy to eradicate residual disease.

In hematological malignancies:

- ***Induction***: the 1st line treatment that is uses very high doses of drug with an aim to kill most of tumor cells; this phase has the most side effects.
- ***Consolidation***: done to eradicate residual disease
- ***Maintenance***: lowest dose of possible chemotherapy to prevent recurrence.

Adjuvant Chemotherapy

- Systemic chemotherapy after primary therapy: surgery, radiation
- Adjuvant chemotherapy immediately follows primary therapy and results in a low disease burden hence preventing recurrence.

Neo – adjuvant Chemotherapy

- This is therapy given before primary treatment: surgery, radiation
- The aim of neo – adjuvant therapy is to:
  - Reduce of tumor mass
  - Lessen amount of radical surgery
- Challenges:
  - Patient may experience toxicities that may delay surgery (primary therapy).
  - May impair post – surgical wound healing as skin cells (rapidly dividing) will be affected

Targeted Agents

- Monoclonal antibodies
- Tyrosine kinase inhibitors.

Monoclonal Antibodies

- They are mostly IgG type antibodies that are directed at specific receptors & block ligands from binding.
- They result in antibody- & complement- mediated cell toxicity.
- Minimal toxicity to non – cancer cells as they are directed towards an antigen (that may not be expressed in non – cancer cells).
- Selectively targeted cancer pathways:
  - Epidermal Growth Factor Receptor (EGFR): cetuximab
  - HER2/neu: trastuzumab
  - Vascular Endothelial Growth Factor (VEGF): bevacizumab

Tyrosine Kinase Inhibitors

- Inhibit tyrosine kinase activation
  - Imatinib mesylate: CML
  - Erlotinib: NSCLC
  - Sorafenib: HCC
  - Sunitinib: GIST

Other Targeted Agents

- ***Histone deacetylase (HDAC) inhibitors:*** enzyme that allows DNA to maintain structural integrity → ***Romidepsin*** (T Cell lymphoma)
- ***Proteasome inhibitor***: affect protein synthesis → ***Bortezomib*** (MM)
- ***mTOR inhibitors → Everolimus*** (Breast Cancer)
- ***Miscellaneous → Thalidomide*** (MM)

Endocrine Therapy

- Treat cancers which are hormone-sensitive
  - Blocking receptors
  - Eliminating endogenous hormone
- Examples:
  - Anti – estrogen drugs in breast cancer
  - Anti – androgen drugs in prostate cancer

Cont.

- Androgens: Fluoxymesterone
- Antiandrogens: Bicalutamide
- Anti – estrogens: Tamoxifen
- Aromatase inhibitors: Anastrozole
- Estrogens: Ethinylestradiol
- GnRH: Goserelin

Biologic Response Modifiers

- Substances that boost immune system to fight cancer:
  - Monoclonal antibodies
  - Vaccines
  - Growth factors (interferon-α, interleukin 2)

Vaccines

- Stimulate body's immune response e.g. Sipuleucel – T (metastatic Prostate cancer)

INTERFERON-α

- Anti – tumour activity by:
  - Anti – proliferative
  - Immunomodulatory
  - Induction of tumor cell antigens
  - Differentiating
  - Anti – angiogenic

Interleukin 2

- Anti – tumour activity by:
  - Stimulation of T- and B-cell proliferation
  - Lysis of tumor cells

Administration - Systemic

- IV route:
  - Most common
  - Bolus injection (<15 minutes)
  - Short infusion (15 minutes to hours)
  - Continuous infusion (24 hours to weeks)
- Can be given oral, IM, S/C

Administration – Regional, Local

- Allows a high concentration at site of tumor
- Reduce systemic exposure (toxicity)
- ***Local drug administration does not target micro – metastases***
- Examples:
  - Intrathecal or intraventricular
  - Intra – vesicular: for early stage bladder cancer
  - Intraperitoneal: for peritoneal carcinomatosis
  - Intra – pleural
  - Chemo – embolization: Trans – Arterial Catheter Chemo Embolization (TACE) in HCC

Common acute toxicities

- Occur either during chemo or 1 – 2 weeks after chemotherapy.
- Are common to all classes of chemotherapeutic agents.
- Include:
  - Myelosuppression
  - Coagulopathies
  - Systemic toxicity: GIT, CNS, CVS, Dermatologic, Nephrotoxicity, Hepatotoxicity

1. Myelosuppression

- Agent-related factors:
  - Specific agent
  - Dose intensity
  - Dose density
- Half life of:
  - RBCs: 120 d
  - Platelets: 7 d
  - WBC: 24 hrs.
    - MC: neutropenia

Cont.

- Host factors:
  - Age: Younger are better as have more cellular marrow
  - Bone marrow reserve
  - Prior chemo – radiotherapy
  - Hepato – renal function: Ability to metabolize and excrete drugs

Cont.

- Phase – specific (esp. S – phase drugs e.g. antimetabolites) cause rapid cytopenias with rapid recovery.
- ***Nitrosoureas***: severe, delayed suppression (6 wk)
- Most regimens given every 3 to 4weeks to allow the BM to recover for the subsequent cycle.
- Targeted therapies are not severely myelo – suppressive.

Prevention of Neutropenia

- Reduce dose of each agents. This may compromise response.
- Prophylactic administration of ***colony stimulating factors 24 hrs. after chemotherapy*** to enhance neutrophil recovery after chemotherapy.
  - G – CSF (MC administered)
  - GM – CSF
- If given prior to chemotherapy may result in formation of immature myeloblasts that are prone to mutations and later development of leukemias in life.

Anaemia

- This is not a dose – limiting toxicity
- Cause is inhibition of DNA synthesis resulting in anisocytosis, macrocytosis. Commonly seen with:
  - Anti – metabolites
  - Hydroxyurea
- EPO ameliorates anemia & reduces the need for transfusion
  - Epoetin alfa, darbepoietin alfa
  - There is a risk for thromboembolic events.

Coagulopathies

- Due to:
  - Chemotherapy-induced thrombocytopenia or thrombosis.
  - Treatment with ***asparaginase*** (inhibition of fibrinogen).

Thrombosis

- Associated with anti – angiogenic therapies:
  - ***Thalidomide***
  - ***Lenalidomide***
  - Bevacizumab
- If patients are on this drugs, administer concomitant aspirin or warfarin to prevent thrombosis.

GIT

- ***Nausea, vomiting: MC A/E of chemotherapy***
  - Can be immediate, delayed (>1week), anticipatory
  - Chemotherapy drugs are divided according to the level of emetogenicity and appropriate anti – emetic therapy should be administered as N & V affects chemotherapy adherence.
- Xerostomia
- Mucositis, stomatitis
- Esophagitis
- Diarrhea
- Constipation
- Malabsorption

Dermatologic

- Alopecia
- Hyper – pigmentation
- Radiation recall
- Photosensitivity
- Nail changes
- Hand – Foot Syndrome
- Acneiform rashes
- Hypersensitivity reactions
- Extravasations

CNS

- Acute Encephalopathy
- Chronic Encephalopathic Syndrome
- Cerebellar Neuropathy
- Peripheral Neuropathy
- Cranial Neuropathy
- Arachnoiditis: Intrathecal Therapy)
- Autonomic Neuropathy
- SIADH

CNS

TABLE 90-8
Neurotoxicity of Selected Chemotherapeutic Agents

Acute Encephalopathy	Chronic Encephalopathic Syndrome	Cerebellar Neuropathy	Peripheral Neuropathy	Cranial Neuropathy	Arachnoiditis (Intrathecal Therapy)	Autonomic Neuropathy	SIADH
Asparaginase	Cytarabine	Cytarabine	Bortezomib	Fluorouracil	Cytarabine	Vinblastine	Cyclophosphamide
Cisplatin	Methotrexate	Cisplatin	Cisplatin	Ifosfamide	Methotrexate	Vincristine	Vinblastine
Cytarabine	Nelarabine	Fludarabine	Docetaxel		Thiotepa	Vinorelbine	Vincristine
Fludarabine	Thiotepa	Fluorouracil	Fluorouracil				Vinorelbine
Ifosfamide		Ifosfamide	Ifosfamide				
Methotrexate			Lenalidomide				
Nelarabine			Nelarabine				
Procarbazine			Paclitaxel				
			Thalidomide				
			Vinblastine				
			Vincristine				
			Vinorelbine				

CVS

- Cardiomyopathy: common with anthracyclines (doxorubicin, daunorubicin), trastuzumab
- Arrhythmias
- Hypertension: Bevacizumab
- Angina & Myocardial Infarction: fluorouracil

Renal

- Nephrotoxicity: Cisplatin
  - Ensure well hydration before, during & after chemotherapy.
  - For cisplatin: also administer mannitol +/- furosemide to ensure the drug does not concentrate in the renal cortex and is flushed out
  - Cisplatin can also cause electrolyte disturbances. Patients may require dialysis so be careful.
- Proximal tubule dysfunction
- Proteinuria: Bevacizumab
- Acute tubular obstruction: Methotrexate
- Haemorrhagic Cystitis: cyclophosphamide

Pulmonary

- Bleomycin:
  - Highest incidence
  - Interstitial pneumonitis
  - Pulmonary fibrosis
- Less with chlorambucil, cyclophosphamide

Hepatotoxicity

TABLE 90-12

Hepatotoxicity From Select Antineoplastic Drugs

Drug	Type
Asparaginase[288–290]	Hepatocellular fatty metamorphosis
Busulfan[291]	Veno-occlusive disease
Carmustine[292,293]	Hepatocellular
Clofarabine[294]	Hepatocellular
Cytarabine[295]	Cholestatic
Etoposide[296]	Hepatocellular
Imatinib[297]	Hepatocellular
Mercaptopurine[298,299]	Cholestatic and hepatocellular
Methotrexate[300,301]	Hepatocellular
Streptozocin[302]	Hepatocellular

Long term complications

- Occur years after receiving chemotherapy.
- Include:
  - Second malignancies
  - Infertility
  - Teratogenicity

Second Malignancies

- AML is seen after combination chemotherapy:
  - Topoisomerase inhibitors: etoposide, anthracyclines)
  - Alkylating agents : melphalan
  - Occur 1 to 3 years after chemotherapy & has a worse prognosis due to mutations in stem cells.
- Superficial bladder cancer in patients taking daily oral cyclophosphamide.

Infertility – oogenesis

- In females, oogenesis is affected.
- Gonadotoxic chemotherapeutic agents:
  - Alkylating agents (most gonadotoxic)
  - Vinblastine
  - Etoposide
  - Cisplatin
- Give gonad sparing options to women of reproductive age or suggest oocyte conservation.

Infertility - Spermatogenesis

- In males there is progressive dose – related depletion of germinal epithelium (azoospermia). This is seen with:
  - Alkylating agents (procarbazine is most gonadotoxic)
  - Doxorubicin
  - Vinblastine
  - Cytarabine
  - Cisplatin

Teratogenicity

- Explicitly discouraged from conception.
  - Wait 2 years after completion of chemotherapy before attempting to conceive.
- When starting chemotherapy in a WRA, ensure a pregnancy test is done and advice on double contraception.

PRINCIPLES OF CANCER CHEMOTHERAPY

BY: DR. INDALO

TYPED BY NAILA KAMADI

DEFINATIONS

- Cytotoxic means being destructive to cells
- Neoplasm means ‘new formation’ (is another word for tumour)
- Neoplasia is a process producing neoplastic disease i.e. formation of new tissue with different character to that already present

NEOPLASTIC CHANGE

GROWTH:

Gene controlled repression

- **Embryonic cell → mature cell**

(proliferating) (switches off growth) (resting)

REGENERATION (due to damage):

controlled

- **Resting cell → proliferating cell**

De-repression

ONCOGENESIS (carcinogenic effect)

- Normal cell → (Uncontrolled) → neoplastic cell
- Neoplastic cell → (De-repression) → spreading population

spreading population

e.g leukaemia OR colony (tumour) e.g breast cancer

metastasis (break up off 1ry colony and continues growing alone)

Secondary tumour

NATURE OF DISEASE ARISING FROM NEOPLASTIC CHANGE

BENIGN POPULATION:

- Well differentiated (particular cell type) ~ retains similarity to cell of origin
- Well demarcated (a boundary ~ fibrous tissue). Immune system detects abnormality therefore puts up barrier ~ takes up form of tissue or capsule & this is important in surgery
- Tumour growth at site of origin & restricted to that site
- May compress other tissues & interfere with blood supply & crush nerves
- Most brain tumours are benign, compress brain cells & kills them ~ death
- Amenable to surgery & radiotherapy

MALIGNANT POPULATION

- Poorly differentiated ~ reverts to simple cell
- Invassive ~ spread well beyond original site
- Pleomorphic (more than one type [polymorphism] ~ variety of size & shape) The cells become primitive i.e. bear no resemblance to the original tissue
- Metastatic ~ 2nd colonies. Bits break off & are transported to other sites to produce 2ry tumours where they will continue to be invassive & metastas to other sites
- Spread thr' blood & lymphatic system

- If spread by arteries the cells will be carried until the arteries have divided & got narrow i.e. deposited in the lungs
- If by venous blood they are carried to the heart & microcirculation of the heart
- Thr' portal vein is deposited in the liver
- Lymphatic spread e.g. from mammary gland to lymph nodes of the arm pit
- Malignant tumours less amenable to surgery & radiotherapy because of the spread. Must apply chemotherapy for all body neoplasias

Goals of cancer treatment

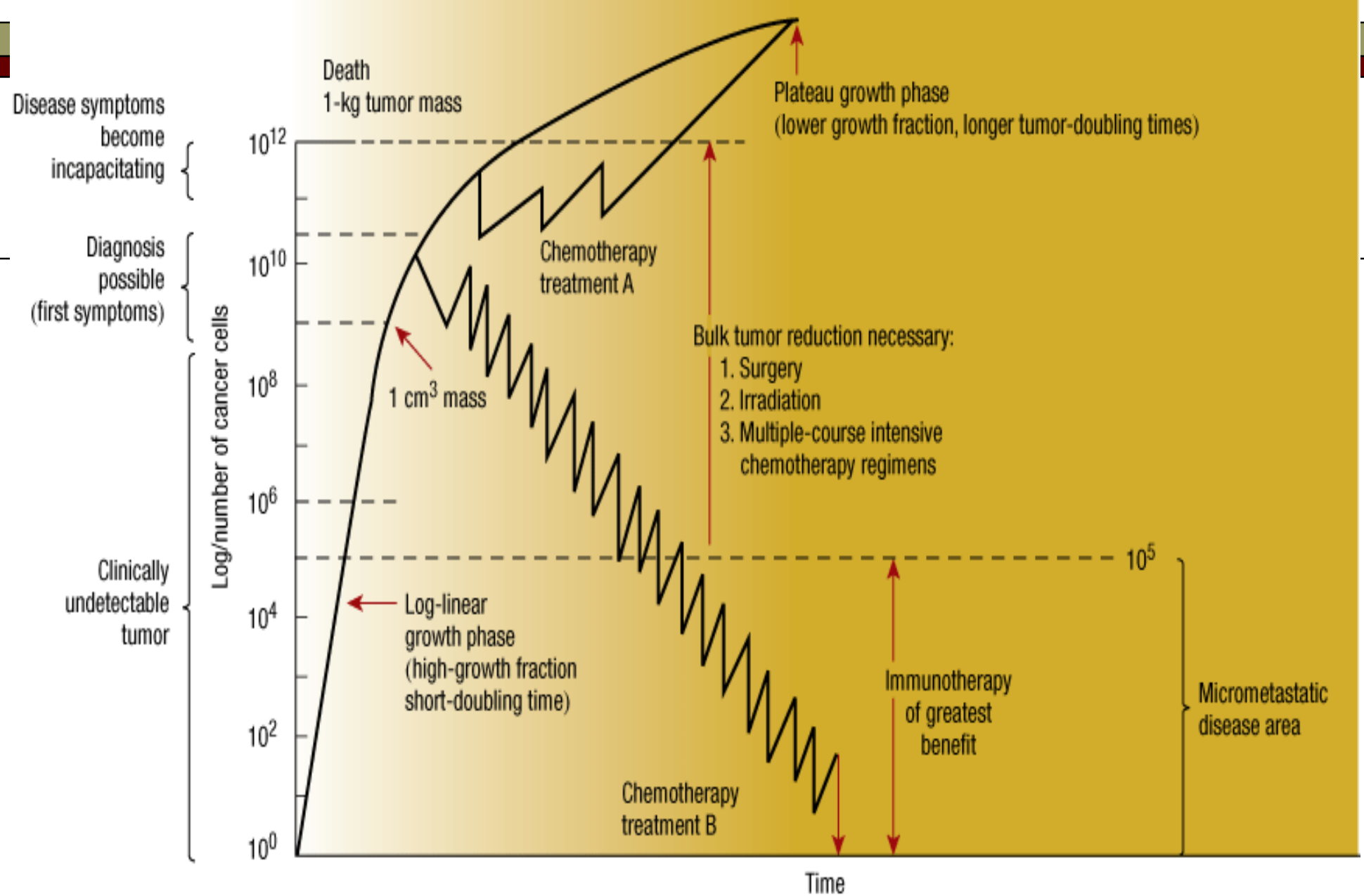
- **Cure the patient - Render him clinically and pathologically free of disease and return their life expectancy to that of healthy individuals of the same age and sex.**
- **To prolong survival while maintaining the patient's functional status and quality of life.**
- **Relive symptoms such as pain for patients in whom the likelihood of cure or prolonged survival is very low**

Pathology of cancer: *tumor origin*

- **Tumors may arise from any of four basic tissue types:-**
  - **epithelial tissue,**
  - **connective tissue (i.e. muscle, bone, and cartilage)**
  - **Lymphoid tissue**
  - **nerve tissue**

Gompertazin growth curve

- **Gompertazin growth curve demonstrates the theoretical pattern of tumor growth**
  - **Tumor growth may be slow very early in the tumor's development, since the tumor cells may have to over come immunological defense mechanisms of the host**



DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A pathophysiologic Approach,* 7th Edition: Http://www.accesspharmacy.com

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Modalities of cancer treatment

The Major Modalities:

- ✓ **Surgery**
- ✓ **Radiation**
- ✓ **Chemotherapy**
- ✓ **Biological therapy**

SURGERY - USES

- To Treat the primary cancer
- To remove isolated metastatic masses
- To make other methods of treatment possible
- Diagnosis and Staging
- Reconstruct anatomical defects to improve function, cosmetic appearance, and quality of life
- Prevention i.e. removal of precancerous lesions such as abnormal moles or colon polyps
- Treat complication e.g. Hemorrhage, Perforation, Bowel obstruction, Spinal cord compression

- **Debulking - Reduce the size of the tumor 1ry to relive pain or other symptoms; Increase effectiveness of radiation or chemotherapy**
- **Surgical removal of a source of hormone - treat tumors whose growth depends on those hormones e.g. removal of testes in prostate cancer and removal of ovaries in breast cancer.**

RADIATION

- Usually administered in small doses over several weeks (fractionating) - permits the administration of levels of radiation sufficient to kill tumor cells while allowing normal surrounding tissue to recover from damage
- Curative radiation is limited to localized tumors like surgery
- Total body radiation to prepare for bone marrow transplant

- As supplement to surgery to destroy micro metastases
- Palliatively e.g. to relieve pain caused by skeletal bone metastases; seizures associated with brain metastases; spinal cord compression caused by growth of tumors on the spine

Chemotherapy

- **Antineoplastic agents are used:**
  - **in the Tx of malignant disease when surgery or radiotherapy are not possible or has proved ineffective.**
  - **as an adjuvant to surgery or radiotherapy**
  - **as in leukaemia the initial Tx**
- **Successful in a few malignant conditions & may be used to palliate symptoms & prolong life in others**

Problem:

- **For most of the time the neoplastic cells are not dividing**
- **They do not divide any more rapidly than normal cells but do it when they shouldn’t i.e. not controlled ~ they are then not more susceptible to the Tx by chemotherapy or radiation than the normal cells ~ low TI**

Kinetics of cell kill

- You can only achieve total ‘cure’ if you have ‘total cell-kill’
- Unlike antimicrobial chemotherapy where there are major contributions by immune mechanisms & other host defenses, these play a negligible role in neoplastic disease unless only a small number of malignant cells are present
- Cytotoxic cell kill follows 1st order kinetics i.e. %age/fraction of cells rather than a constant number of cells are killed by a given therapeutic maneuver

- E.g. 1 kg of cancer harbours 10^{12} malignant cells, a 99.99% kill of cells will reduce mass to 100mg (of tumour) [10^{8} malignant cells]
- The surviving cells may proliferate and clone a line of resistant cells

- Onset of resistance is slow for slow cycling cells
- Rapid cycling cells are killed fast but also build up quick resistance
- Reduction in tumour cell may result in clinical remission but without eradicating the tumour
- NB: the faster the cells divide, the more easily they are killed & the faster the onset of clinical remission & if tumour cells not completely cleared, quickly dividing cells also produce clinical relapse quickly e.g. acute myeloid leukaemia

- Cancer Tx carried out in specialist clinics
- General continuing Tx partly responsibility of surgeons, physicians & general practitioners
- Overall Mx includes:-
  - Mx of patient & family;
  - control of symptoms e.g. pain;
  - Tx of complications
- Drugs have low TI ~ results of toxicity symptomatically distressing & can be fatal
- Choice of Tx based on assessments of its efficacy in similar cases, & on mental, physical & social condition of the individual patient

Site of action

- Cytotoxic drugs act at different sites to interfere with cell growth and division
- Combination drug therapy gives opportunity for producing cumulative biochemical lesions in the cell during drug therapy

The cell cycle

All cells which synthesize DNA go thr' a regular cycle which has several different phases:-

- **G_1 phase - resting phase occurs after cell division (mitosis) complete; no DNA synthesis.**
- **S phase - DNA synthesis; preceded at end of G_1 by an increase in rate of RNA synthesis**
- **G_2 phase - DNA synthesis stops; RNA & protein synthesis continues**
- **M phase (mitosis) - decrease in rate of RNA & protein synthesis**
- **G_0 phase - resting phase**

- **Different cytotoxic drugs may act at different phases of cell cycle.**
- **If faster cell cycle & turn over:**

  - the more likely for cytotoxics to ‘catch’ cells in a sensitive phase

  - the more malignant the condition

  - the normal tissues with fast cell cycles e.g. bone marrow, GIT mucosa, lymphoid tissue & skin suffer most from cytotoxic therapy

- Cell cycle (duration depends on G1 time)

C E L L C Y C L E

DAYS	WEEKS	MONTHS
NORMAL CELLS		
Bone marrow	hair follicle	liver
GIT mucosa	skin basal	kidney
TUMOUR CELLS		
Berkitts	acute leukaemia	colon carcinoma
(germ cell)	(blast cell)	lung cancer

- In colon carcinoma and lung cancer, the cells don't cycle quickly therefore hard to hit
- NB: normal & tumour cells that cycle quickly are more vulnerable to both cycle specific & cycle non-specific drugs

- The more cells there are in the tumour in synchrony of cycle, the more cells will be ‘caught’ by pulse cytotoxic drug therapy
- The fewer the cells in synchrony, the more necessary to prolong therapy with subsequent increase in toxicity
- May attempt to recruit cells into synchrony e.g. surgical removal of large tumour masses may provoke remaining cells to proliferate at which point they may be ‘caught’ by cytotoxic drug therapy (adjuvant chemotherapy to surgery)

Tumour size

- Large tumours relatively unresponsive to cytotoxic Tx because:-
- Many cells tend to be in G_0 phase (resting phase)
- Penetration of drug insufficient (because of poor vasculature) to achieve cytotoxic []s for long enough without producing systemic toxicity
- Based on cell-growth kinetics & vascularity, small tumours tend to be more sensitive to chemotherapy ~ the sooner Tx instituted the better

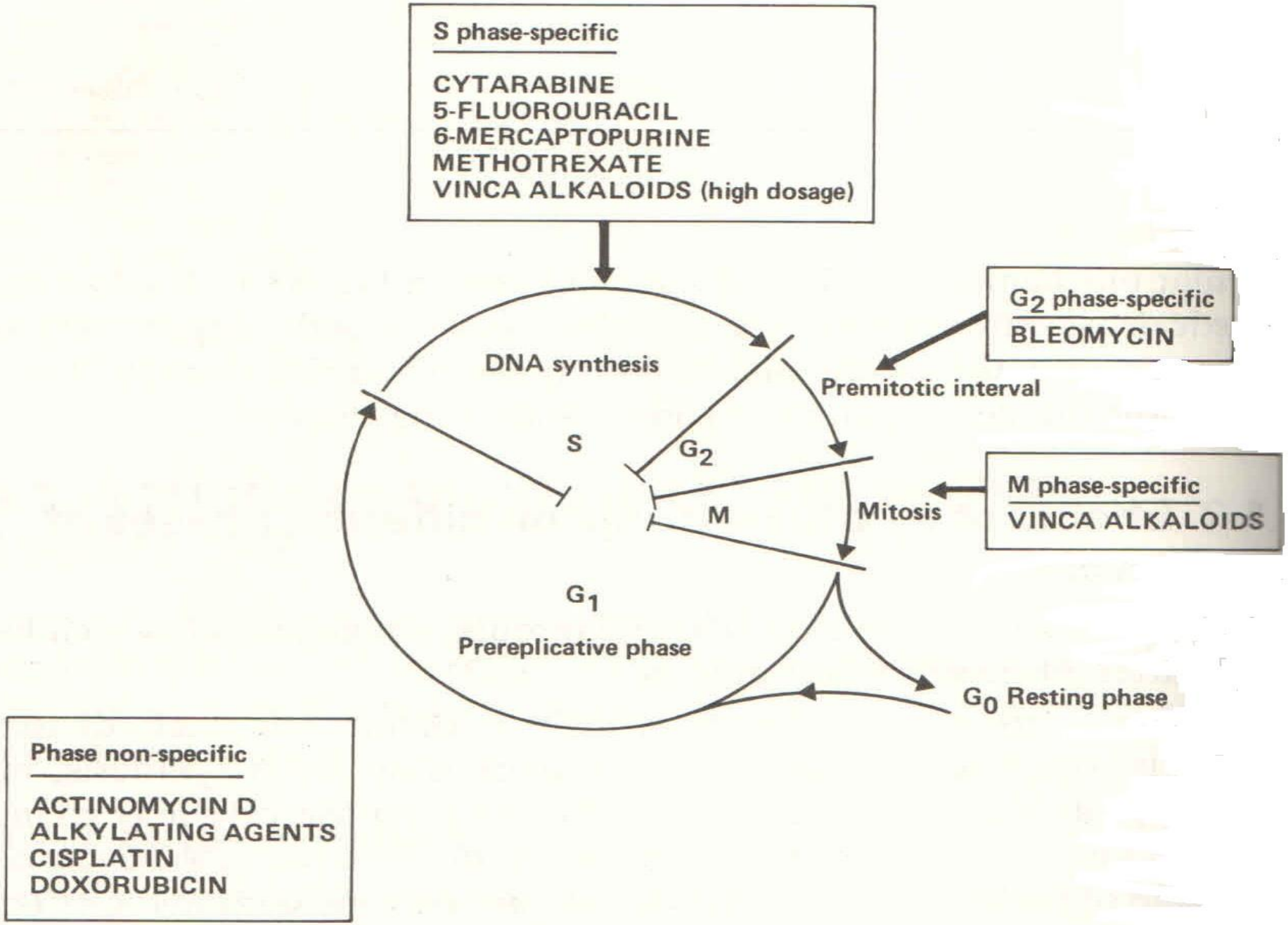
Pre-Tx evaluation

- To evaluate likely response and progress
- Histopathology & clinical staging (by radiological techniques e.g. CAT [computed axial tomographic] scanning, & surgical exploration (e.g. in Hodgkins lymphoma) are essential
- May be repeated during therapy to give guidance as to the advisability for further chemotherapeutic courses
- In some cases measure tumour markers e.g. gonadotropic hormones (choriocarcinoma), myelome proteins, alpha-fetoprotein (hepatocellular carcinoma), acid phosphatase (prostatic carcinoma)

Combination therapy

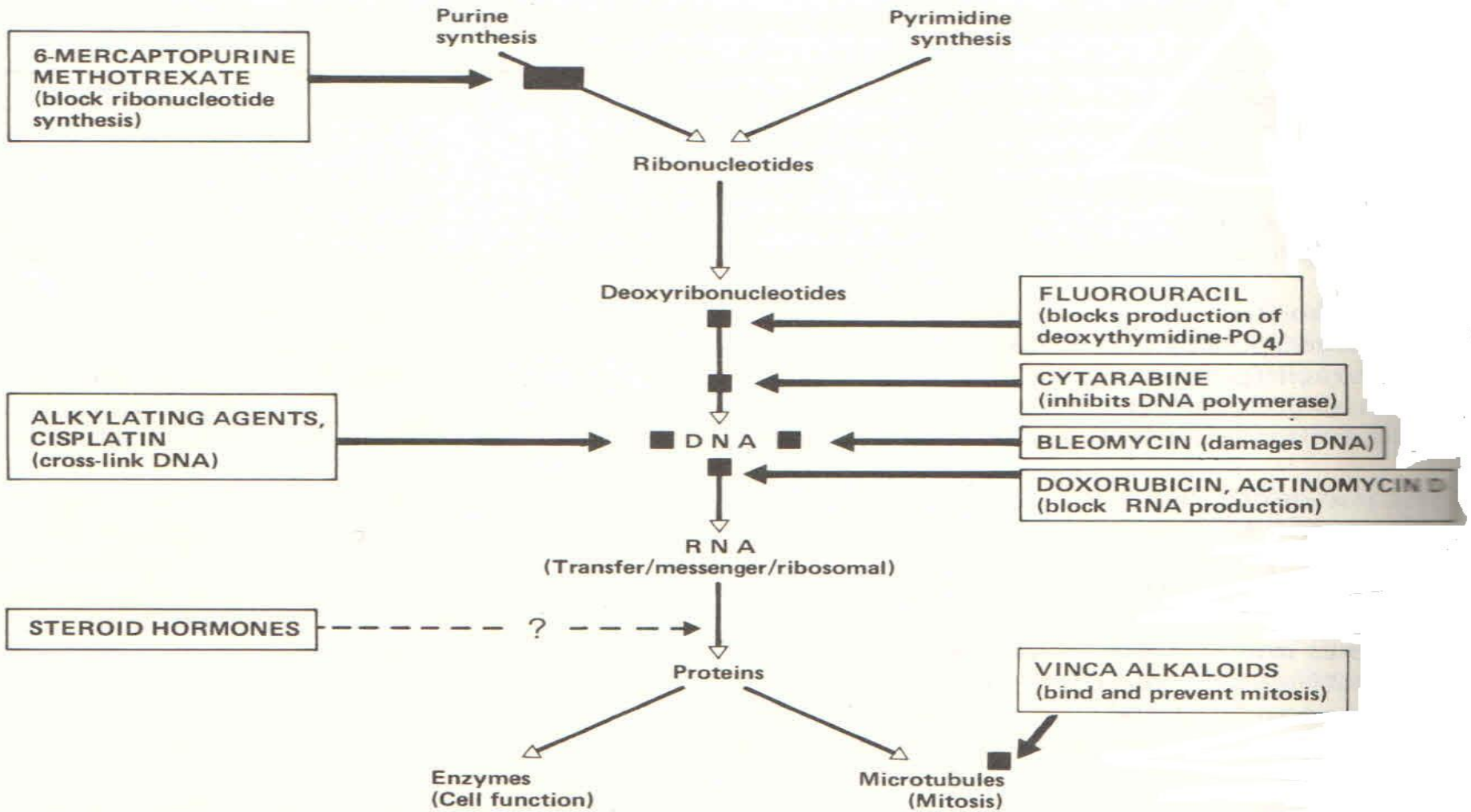
- To circumvent development of drug-resistance to single agents
- To minimize toxicity to individual agents
- Optimize kill of neoplastic cells by applying cell kinetic principles
- Use of additional agents having access to sanctuary sites

NB: Each drug has a known action against particular tumour type



The cell cycle and the timing of the actions of cytotoxic drugs.

The principles of cancer chemotherapy



Cellular molecular biochemistry and the sites and mechanisms of action of cytotoxic drugs.

Regimens of cancer chemotherapy

- AIM: Get enough drug to the tumor cells for long enough to achieve a reasonable kill while avoiding unacceptable toxicity
- Most regimens based upon intermittent admn of drugs with intervals of a few weeks between courses ~ allows recovery of normal bone marrow & immune functions between courses
- Daily admn e.g. diethylstilboestrol for carcinoma of the prostate; busulphan for chronic myeloid leukaemia
- Monthly (28 days) admn e.g. s/c inj goserelin for carcinoma of the prostate

- **Special action to get drugs to sites not easily accessible to systemically administered drugs:-**
  - **e.g. instillation of thiotepa into pleural or peritoneal malignant effusions ~ can be palliative, reducing the size of the effusion;**
  - **e.g. intrathecal methotrexate & radiotherapy to the cranium in preventing CNS (sanctuary site) involvement in acute lymphoblastic leukaemia in children**

Adverse effects of cytotoxics

- Occurrence of adverse effect limits the use of cytotoxic drugs
- Normal cells that cycle fast are most susceptible
- Toxicity exerted particularly against dividing cells
- The toxicity is a function of their therapeutic activity
- Adverse effects include:

  Nausea & vomiting; bone marrow toxicity, GIT toxicity skin, Gonadal effects, Nervous tissue, Hyperuricaemia Carcinogenesis & mutagenesis

Special adverse effects of individual drugs

- Cyclophosphamide - haemorrhagic cystitis
- Bleomycin - pulmonary fibrosis
- Busulphan - pulmonary fibrosis
- Vincristine - peripheral neuropathy
- Vincristine - autonomic neuropathy
- Doxorubicin - cardiac arrhythmias
- Doxorubicin - cardiomyopathy
- 5-fluorouracil - skin pigmentation
- Methotrexate - hepatic damage (chronic Tx)

Drug interactions

- Immune responses may be diminished ~ risk of using live vaccines→ may get exaggerated local rn to the vaccine or severe systemic infection e.g. reported after small pox vaccination in patients taking methotrexate

OTHER THAERAPEUTIC MANOUVERS IN CANCER MANAGEMENT

- **Endocrine therapy –**
  - Option for Mx of cancers from tissues whose growth is under gonadal hormonal control e.g. breast, prostate, and endometrial cancers
  - Major organ system toxicity is uncommon from hormonal treatment ~ the least toxic of systemic anticancer therapies.
  - CORTICOSTEROIDS - Play important role in managing hematological malignancies

- **Biological therapy - e.g. immune system therapies such as:**
  - **Interferons,**
  - **Interleukins,**
  - **Colony-stimulating factors (CSFs)**
  - **Monoclonal Antibodies (**MoABs)
  - **Tumor vaccines**
  - **Gene therapy**

- **Combination of chemotherapy with biological therapy**
- **Angiogenesis inhibitors**

Administration of chemotherapy

- WBC count 3,000/mm^3 or an ANC of 1,500/mm^3 and a platelet count of 100,000/mm^3 usually required prior to administering chemotherapy.
- Assess renal and hepatic function, especially for agents eliminated via those routes.
- Chemotherapy dosed based on body surface area - used as an estimate of cardiac output and subsequent distribution to the liver and kidneys

BODY SURFACE AREA (BSA) FORMULA

THE MOSTELLER FORMULA:-

BSA (m^2) = SQRT ([Height(cm) x Weight(kg)] / 3600)
e.g. BSA = SQRT (cm*kg)/3600

(SQRT is Square Root)

Or in inches and pounds:-
BSA (m^2) = SQRT ([Ht(in) x Wt(Lbs)] / 3131

Evaluation of response to Ca Tx

- Complete response or remission (CR)
- Partial response (PR)
- Disease progression (treatment failure)
- Stable disease
- Clinical benefit response status.

Evaluation of response …..

Survival end points:

- Overall survival
- Disease-free survival
- Progression-free survival

Factors affecting response to chemotherapy

- Tumor burden
- Tumor-cell heterogeneity
- Drug resistance
- Dose intensity
- Patient-specific factors.

The relationship between dose and response

- The delivery of optimal dose intensity is often compromised by the toxicities of the oncologic drugs.
- Treatment cycles are commonly delayed because of inadequate recovery from drug toxicity, especially myelosuppression.
- Subsequent doses of chemotherapy are often reduced to prevent or reduce the severity of these toxicities.

The sun will rise & we will try again tomorrow.

#Perseverance

#Jesus_Is_Reliable_Strength☺

9. INFECTIOUS DISEASE THERAPEUTICS LEVEL VI MBCHB 2019

COMPILED BY NAILA KAMADI

Outline

Rational use of antibiotics

Anti – Retroviral Therapy

Treatment of opportunistic infections in HIV

1. RATIONAL USE OF ANTIBIOTICS

BY: DR. OMONGE

TYPED BY NAILA KAMADI

Introduction

- Appropriate use of:
  - Drug of choice
  - Dose
  - Route of administration/ delivery
  - Duration
  - De – escalation

Optimizing antibiotic selection

- Know your patient
- Know the causative bug
- Know the appropriate drug
- Know your local epidemiology (***anti – biogram***)

Case study 1

- GM ***32 y/o male*** is seen at the outpatient department with ***7 days history of dull left chest pain & productive cough with scanty mucoid sputum.***
- GM has ***been well with no previous illness or hospital***
- He reports ***fever***, ***general malaise***, ***headache*** and ***joint patients***
- He has ***no history of rhinorrhea or sore throat*** (not a viral illness since they give catarrhal symptoms e.g. conjunctivitis)

Examination findings

- Temp: 37.8^0C
- BP: 115/75
- Pulse: 80/min regular
- RR: 20/ min
- Acyanotic, no lymphadenopathy, no conjunctivitis
- Auscultation reveals sparse crepitations on the left mid & lower chest
- ***Vitals are demonstrating that the bug is atypical since the fever is not accompanied by tachycardia hence the inflammatory process evoked is not intense.***

Lab tests

- Blood sugar & U/E/Cs are normal
- Blood cultures and sputum examination are requested
- CXR is done
- Diagnosis: ***Community acquired pneumonia***

Patient risk stratification bundle

	Type 1	Type 2	Type 3
Health care contact	No	Yes	Prolonged
Procedures	No	Minimum	Major invasive procedures
Antibiotic Rx history	No in the last 90 days	Yes in the last 90 days	Repeat multiple antibiotics
Patient characteristics	Young: no comorbid conditions	Elderly; few comorbid conditions	ISS or with many co – morbid conditions
Causative pathogen could be:	Susceptible to common narrow spectrum antibiotics	Extended Spectrum β – Lactamases (ESBLs) → produced by E. coli & Klebsiella spp.	ESBLs/ Pseudomonas/ Acinetobacter MRSA
Possible antibiotic recommendations	No need for BSAs	Use non – pseudomonal BSAs	Use anti – pseudomonal BSAs

Risk factors for MDR infection

- Hospitalization for ≥ 5 days.
- Admission from another facility.
- Antibiotic use within 3 months prior to admission.
- Immunosuppression.
- Reported high frequency of MDR organisms in the unit.

Knowing the bug

- Gram negative vs. Gram positive cell wall
  - ***Gram negative***: outer lipopolysaccharide membrane, peptidoglycan, penicillin binding proteins (PBPs), inner cytoplasmic membrane
    - Have more virulence factors and hence are responsible for most cases of sepsis.
  - ***Gram positive***: no outer membrane, peptidoglycan

Beta lactamases Ambler classification

- A: ISBL; Extended spectrum β – lactamases (EBL)
- B: Metallo β – lactamases (MBL)
- C: Amp – C
- D: Oxacillinases

Note

- Penicillinases: once penicillinases are directed against cephalosporins (i.e., cephalosporinases) they are ESBLs.
- Resistant mechanisms of fluoroquinolones develop very rapidly hence use ciprofloxacin carefully.

MDR gram negative enterobacteriaceae

- These include 3rd generation cephalosporin resistant ***E. coli*** & ***Klebsiella***
- Mechanism
  - ESBL production
  - Hyper – production of Amp C
  - CPE?, KPC – kp, OXA 48

MDR gram negative non – lactose fermenters

- Varying incidence worldwide: MDR *P. aeruginosa*
- Resistance to ≥ 3 classes: ***aminopenicillins***, ***cephalosporins***, ***carbapenems***, ***aminoglycosides***, ***quinolones***
- Multiple resistant mechanisms (organisms with all these tend to be XDR – PA)
  - Inducible Amp C BL
  - Efflux pump
  - Loss of porin channels
  - Aminoglycoside modifying enzymes
- Example: ***Acinetobacter spp***.

Features of suitable antibiotics

- Small enough to pass through the porin channels
- Stable enough to resist degradation by beta lactamases
- Lipid soluble

Hydrophilic vs. lipophilic antibiotics

Hydrophilic Antibiotics: beta lactams, aminoglycosides, glycopeptides

- **General PK**
  - Smaller Vd
  - Predominantly renally cleared
  - Low intracellular penetration
- **Altered PK**
  - Increased Vd
  - Clearance increased/ decreased dependent on renal function and protein binding

Lipophilic Antibiotics: FQs, macrolides, rifampicin, linezolid

- **General PK**
  - Larger Vd
  - Predominantly hepatic cleared
  - Good intracellular penetration
- **Altered PK**
  - Vd largely unchanged
  - Clerance increased/ decreased dependent on hepatic function and protein binding

PK/PD parameters

- Predictors of bacterial eradication: PK/ PD profiles
- There are 3 types of ABS
  1. ***Concentration dependent antibiotics*** (Peak/MIC) → aminoglycosides, metronidazole (> 8 – 10 MIC)
  2. ***Time dependent antibiotics*** (Time above MIC) → beta lactams, clindamycin, erythromycin, linezolid (through to MIC 4 – 6 TDM)
     1. Never use these drugs OD unless time above MIC can be achieved with one dose; 40 – 60% of the time above MIC
  3. ***Concentration & Time dependent***: azithromycin, quinolones, vancomycin, teicoplanin (25 – 125)

Note

- Trough levels, rather than peak levels, are responsible for toxicity.

Factors to consider when deciding whether your drug appropriate?

- Disease sanctuary: is the drug able to get to the disease sanctuary? E.g. blood in septicemia, CSF in meningitis etc.
- Drug choice
- Dose
- Delivery
- Disposition of the drug: hepatic vs. renal
- Duration of therapy
  - > 7 days: meningitis, prostatitis, pyelonephritis, osteomyelitis etc.
- Drug – drug interaction

Why do Carbapenems have enhanced activity?

- Smaller molecule size
- Zwitterionic properties, facilitate rapid penetration across GNB membrane
- High affinity for essential PBPs
- Resistance to a broad range of beta lactamases

Further reading

- Mechanism of action of antibiotics.
- Management of gram negative infections:
  - Appropriate selection of antibiotics.
- Management of severe sepsis & septic shock
  - Take into account the augmented renal clearance present in this condition.

2. ANTIRETROVIRAL THERAPY 12/3/2019

BY: DR. GICHUHI

TYPED BY NAILA KAMADI

Introduction

- Human immunodeficiency virus (HIV) is the cause of acquired immunodeficiency syndrome (AIDS).
- HIV is one of the two important human T – cell lymphotropic retroviruses (human T – cell leukemia virus is the other).
- HIV preferentially infects & **kills helper (CD4) T lymphocytes,** resulting in the loss of CMI & a high probability that the host will develop **opportunistic infections (OIs).**
- Both HIV-1 & HIV-2 cause AIDS, but HIV-1 is found worldwide, whereas HIV-2 is found primarily in West Africa.

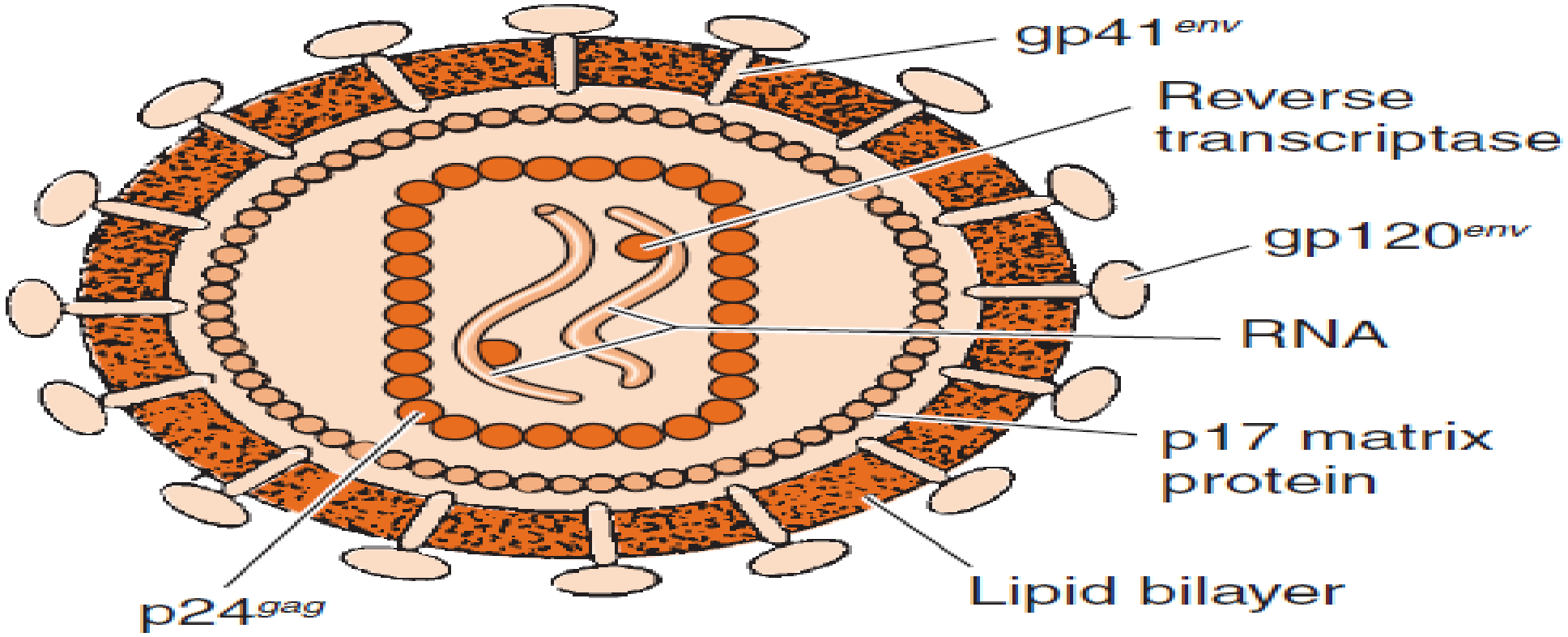


FIGURE 45–2 Cross-section of HIV. In the interior, two molecules of viral RNA are shown associated with reverse transcriptase. Surrounding those structures is a rectangular nucleocapsid composed of p24 proteins. Note that the viral protease and integrase are also located within the nucleocapsid (in addition to the reverse transcriptase), but, for lack of space, are not shown in the figure. On the exterior are the two envelope proteins, gp120 and gp41, which are embedded in the lipid bilayer derived from the cell membrane.
(Reproduced with permission from Green WC. Mechanisms of disease: the molecular biology of human immunodeficiency virus type I infection. *NEJM*. 1991;324(5):309.)

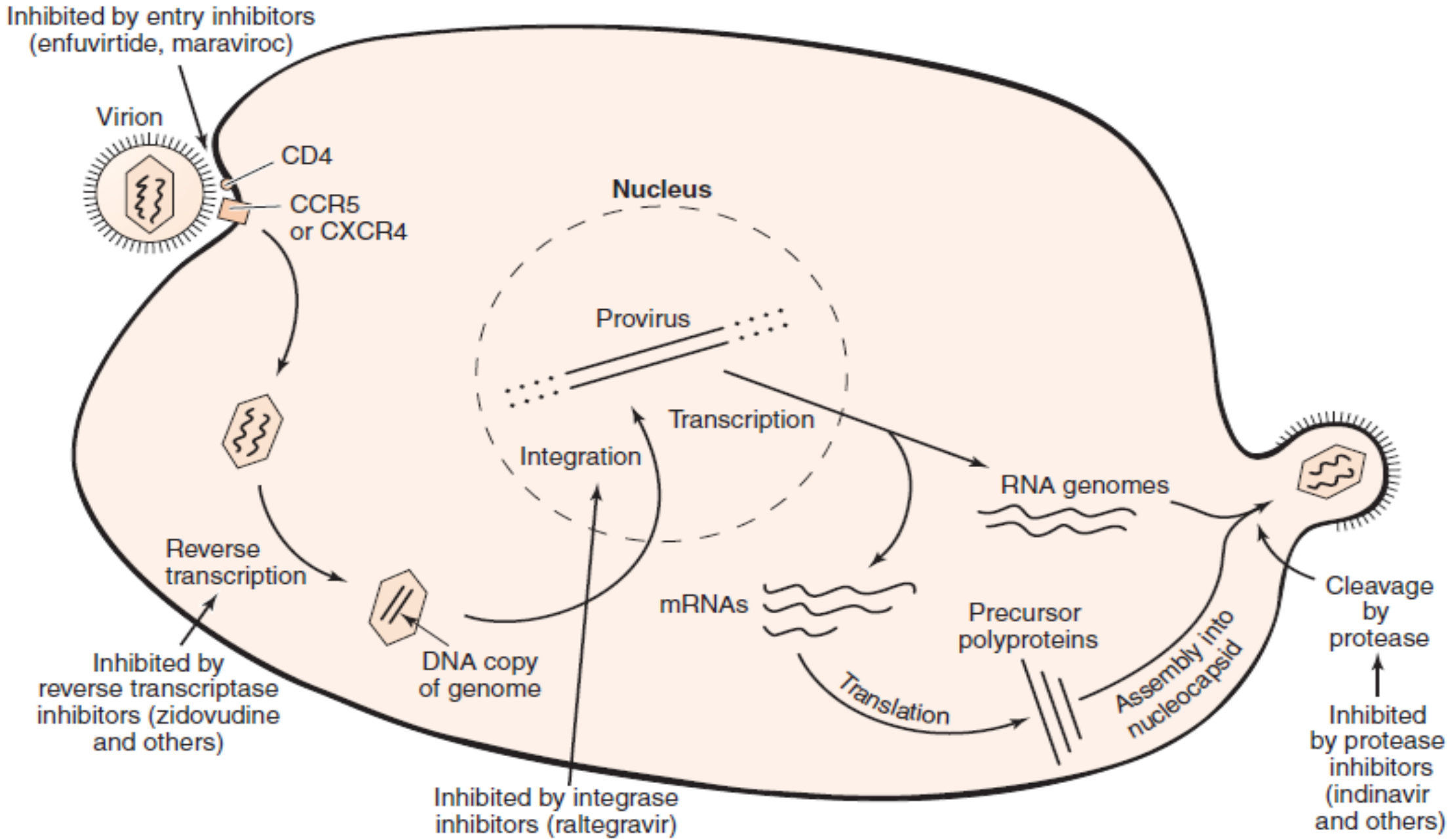


FIGURE 45–4 Replicative cycle of HIV. The sites of action of the important antiviral drugs are indicated. The mode of action of the reverse transcriptase inhibitors, entry inhibitors, the integrase inhibitor, and the protease inhibitors is described in Chapter 35. (Modified and reproduced

Classification of Anti – Retroviral Drugs

- **Nucleoside Reverse Transcriptase Inhibitors (NRTIs):**
  - Zidovudine (ZDV, AZT)
  - Lamivudine (3TC)
  - Emtricitabine (FTC)
  - Abacavir (ABC)
- **Nucleotide Reverse Transcriptase Inhibitors (N_tRTIs)**:
  - Tenofovir (TDF)

Cont.

- **Non – Nucleoside Reverse Transcriptase Inhibitors (NNRTIs):**
  - Nevirapine (NVP)
  - Efavirenz (EFV)
  - Etravirine (ETR)
- **Protease Inhibitors (PIs):**
  - Lopinavir (LPV)
  - Ritonavir (RTV)
  - Darunavir (DRV)
  - Atazanavir (ATV)

Cont.

- **Entry inhibitors**
  - Enfuvirtide (T – 20)
  - Maraviroc (MVC)
- **Integrase Strand Transfer Inhibitors (INSTIs)**
  - Raltegravir (RAL)
  - Dolutegravir

NRTI & N_tRTIs

- These are phosphorylated into mono-, bi- or tri- phosphates & then are incorporated into the replicating retrovirus where they block the replication of the virus genome by:
  - Competitively inhibiting the incorporation of native nucleotides.
  - Terminating elongation of proviral DNA because they lack a 3 – hydroxyl group.
- TDF is only phosphorylated twice to form a biphosphate whereas the rest are phosphorylated thrice to form triphosphates.

Cont.

- They also inhibit both HIV – 1 & HIV – 2.
- ***FTC, 3TC*** & ***TDF*** also have activity against ***HBV.***
- ***TDF*** also has activity against ***herpes viruses***.
- ***ZDV*** also has activity against ***the human T cell lymphotropic virus***.

Cont.

- They also inhibit ***DNA polymerase γ*** found in mitochondria hence resulting in toxicity that manifests as:
  - Anemia & granulocytopenia (***mainly caused by ZDV***)
  - Myopathy
  - Peripheral neuropathy
  - Pancreatitis
  - Lactic acidosis
- ***FTC***, ***3TC*** & ***TDF*** have very low affinity for DNA polymerase γ & are therefore devoid of mitochondrial toxicity.

MoA

- ***NNRTIs***: bind to reverse transcriptase & cause a conformational change that reduces enzymatic activity.
- ***Protease inhibitors***: inhibit protease
- ***Integrase inhibitors***: inhibit integrase

Cont.

- ***Entry inhibitors***
  - **Enfurvirtide**: inhibits fusion of the virus & CD4 cells mediated by gp41.
  - **Maraviroc**: prevents gp120 from binding the CCR5 co – receptor of the virus.

When a patient comes into the clinic:

- Confirm that they are HIV +ve.
- Determine the WHO clinical stage.
- History & PE
  - Take a drug history
    - Look out for traditional, non – prescription medications as well as previous ARV use
  - Alcohol & cigarette use: may not be adherent to HAART.
  - Start on **cotrimoxazole** & **multivitamins**.
  - Detect & treat opportunistic infections.

WHO Clinical Staging of HIV Infection in **Infants & Children** (confirmed by serology or DNA PCR)

Stage I

- Asymptomatic
- Persistent generalized lymphadenopathy (PGL)
- Unexplained, asymptomatic hepatosplenomegaly

Stage II

- Papular pruritic eruptions (PPE)
- Seborrheic dermatitis
- Fungal nail infections
- Angular cheilitis
- Linear gingival erythema
- Extensive HPV or molluscum infection (>5% of body area/face)
- Recurrent oral ulcerations (>2 episodes/ in 6 months)
- Parotid enlargement
- Herpes zoster (>1 episode/12 months)
- Recurrent or chronic upper respiratory infection (URI): otitis media, otorrhoea, sinusitis (>2 episodes/6 months)

Stage III

- Unexplained moderate malnutrition (-2SD or Z score) not responding to standard therapy
- Unexplained persistent diarrhoea (>14 days)
- Unexplained persistent fever (intermittent or constant, > 1 mo.)
- Oral candidiasis (outside neonatal period)
- Oral hairy Leucoplakia
- Pulmonary tuberculosis
- Severe recurrent presumed bacterial pneumonia (>2 episodes/12 months)
- Acute necrotizing ulcerative gingivitis/ periodontitis
- Lymphoid interstitial pneumonitis (LIP)
- Unexplained anaemia (<8g/dL), neutropenia (<1,000/mm^3), or thrombocytopenia (<30,000/$mm^{3)}$ for >1 mo.
- HIV-related cardiomyopathy
- HIV-related nephropathy

Stage IV

- Unexplained severe wasting or severe malnutrition (-3 SD or Z score) not responding to standard therapy
- Pneumocystis pneumonia
- Recurrent severe bacterial infections (>2 episodes/12 months, excluding pneumonia)
- Chronic orolabial or cutaneous HSV (lasting > 1 mo)
- Extra-pulmonary tuberculosis
- Kaposi's sarcoma
- Oesophageal candidiasis
- CNS toxoplasmosis
- Cryptococcal meningitis
- Any disseminated endemic mycosis
- Cryptosporidiosis or Isosporiasis (with diarrhoea > 1 month)
- CMV infection of organ other than liver, spleen, lymph nodes (and onset age >1 month)
- Disseminated mycobacterial disease other than tuberculosis
- Candida of trachea, bronchi or lungs
- Acquired recto-vesicular fistula
- Cerebral or B-cell non-Hodgkin's lymphoma
- Progressive multifocal leucoencephalopathy (PML)
- HIV encephalopathy

WHO Clinical Staging of HIV infection in **Adolescents & Adults**

Stage 1

- Asymptomatic
- Persistent Generalized Lymphadenopathy (PGL)

Stage 2

- Moderate unexplained weight loss (< 10% of presumed or measured body weight)
- Minor mucocutaneous manifestations (seborrheic dermatitis, papular pruritic eruptions, fungal nail infections, recurrent oral ulcerations, angular cheilitis)
- Herpes zoster
- Recurrent upper respiratory tract infections (sinusitis, tonsillitis, bronchitis, otitis media, pharyngitis)

Stage 3

- Unexplained severe weight loss (over 10% of presumed or measured body weight)
- Unexplained chronic diarrhoea for longer than one month
- Unexplained persistent fever (intermittent or constant for longer than one month)
- Persistent oral candidiasis
- Oral hairy leukoplakia
- Pulmonary tuberculosis
- Severe bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)
- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
- Unexplained anaemia (below 8 g/dl), neutropenia (below 0.5 x 109/l) and/or chronic thrombocytopenia (below 50 x 109 /l)

Stage 4

Conditions where a presumptive diagnosis can be made using clinical signs or simple investigations:

- HIV wasting syndrome
- Pneumocystis jirovecipneumonia (PCP)
- Recurrent severe bacterial pneumonia (≥ 2 episodes within 1 year)
- Cryptococcal meningitis
- Toxoplasmosis of the brain
- Chronic orolabial, genital or ano-rectal herpes simplex infection for > 1 month
- Kaposi's sarcoma (KS)
- HIV encephalopathy
- Extra pulmonary tuberculosis (EPTB) Conditions where confirmatory diagnostic testing is necessary:
- Cryptosporidiosis, with diarrhoea > 1 month
- Isosporiasis
- Cryptococcosis (extra pulmonary)
- Disseminated non-tuberculous mycobacterial infection
- Cytomegalovirus (CMV) retinitis or infection of the organs (other than liver, spleen, or lymph nodes)
- Progressive multifocal leucoencephalopathy (PML)
- Any disseminated mycosis (e.g. histoplasmosis, coccidiomycosis)
- Candidiasis of the oesophagus or airways
- Non-typhoid salmonella (NTS) septicaemia
- Lymphoma cerebral or B cell Non-Hodgkin's Lymphoma
- Invasive cervical cancer
- Visceral leishmaniasis
- Symptomatic HIV-associated nephropathy or HIV associated cardiomyopathy

Cont.

- Psychosocial assessment
  - HIV education & psychological support
  - Assess willingness to start HAART
  - Offer support groups
  - Offer to help with disclosure to partners
- Adherence counselling

Cotrimoxazole (Septrin)

- Is to be taken for the whole lifetime of the patient.
- Prevents specific OIs for patients with low CD4 counts esp. ***Pneumocystis Carinii Pneumonia & toxoplasmosis***
- Reduces risk for:
  - Common bacterial infections
  - Sepsis
  - Diarrheal illness
  - Malaria

Dapsone – A substitute in severe allergy to septrin

- If the patient is severely allergic to cotrimoxazole or has failed desensitization to cotrimoxazole, dapsone may be used as an alternative but it is only specific to PCP & does not confer the rest of the advantages that cotrimoxazole does.
- It is only recommended if :
  - The patient is in WHO stage 4 &/or
  - CD4 count is $\leq$ 200 cells/mm^3
- Dapsone should be discontinued once a CD4 count of > 200 cells/mm^3 is sustained for $\geq$ 6 months.

Laboratory tests

- These are desirable but they are not a pre – requisite for the initiation & routine monitoring for ART in ***clinically stable patients***.

Baseline tests

- HIV test (mandatory if a documented result is unavailable).
- CD4 cell count
- FHG (if not possible, a hemoglobin may be adequate) & WBC differential.
- Renal Function Tests(Creatinine & Urinalysis)
  - Calculate creatinine clearance: if ≤ 50ml/min then TDF should be avoided unless there is HBV confection.
  - Urinalysis: protein & glucose

Cont.

- HBsAg: immunization for all patients who screen negative even if they have been immunized before.
- HCV antibody for IVDU
- Serum CRAG (If CD4 $\leq$ 200 cell/mm^3)
- RBS
- Pregnancy status: LNMP, if delayed/ irregular do a urine pregnancy test
- RPR or VDRL
- Lipid profile

Cont.

- Other desirable baseline tests:
  - To assess comorbidities & ARV toxicity
  - Baseline viral load: Only recommended for HIV Exposed Infants (HEIs) after the 1st PCR test is +ve.

Cont.

- ALT: This is not a recommended baseline investigations unless there is a specific clinical reason e.g.
  - Patient with a history of hepatitis
  - Signs or symptoms of liver disease
  - Risk of liver disease e.g. alcoholics
  - HBV/HCV coinfection
  - Hepatotoxic drugs

Criteria for initiation of HAART in Kenya 2018

- All people living with HIV (PLHIV) qualify for ART irrespective of:
  - CD4 cell count or percentage
  - WHO clinical stage
  - Age
  - Pregnancy/ breastfeeding status
  - Comorbidities/ coinfections

Cont.

- ART should be initiated as soon as the patient is ready to start, preferably within 2 weeks from the time of HIV diagnosis.
- If pregnant, it is highly advisable that the mother starts treatment on the same day of diagnosis.
- If there is associated **cryptococcal meningitis**: Start Rx 5 weeks after initiation of therapy for the meningitis.
- If there is associated **TB**: Start Rx about 2 – 8 weeks after initiation of anti – TB therapy (depending on whether it is PTB or EPTB).

Goals of ART

- Suppress viral replication to undetectable levels.
- Restoration &/or preservation of immunological function.
- Reduction of HIV – related morbidity & mortality.
- Improvement of patients quality of life (prevent unpleasant adverse effects)
- Prevention of transmission of HIV

Recommended 1st line Rx in Kenya for adults & adolescents

- TDF + 3TC + DTG
  - Not for women of child bearing age because children to women taking DTG developed Neural Tube Defects (NTDs) in Botswana
- OR: TDF + 3TC + EFV
  - ***Report any NTDs observed amongst mothers taking EFV to NASCOP***.

Cont.

- Also pregnant women (at any gestational age)
  - NB DTG (FDA alert 18/5/2018)
  - Reports NTDs
  - Related to first trimester
- Breastfeeding
- TB/ HIV coinfection
- HBV/HIV coinfection

Alternative Rx for first line

- ABC instead of TDF if creatinine clearance is <50ml/in: avoid TDF.
- ATV/r instead of EFV if:
  - The latter is not tolerated or
  - A positive psychiatric history in women of childbearing age
- EFV if DTG is not tolerated

If HIV/TB coinfection

- HAART regimen: ***TDF + 3TC + DTG***
  - Usually a ***fixed dose combination (FDC)*** & administered OD
  - Due to the enzyme inducing effects of rifampicin, *add another dose of DTG*, i.e., additional to the am dose of the FDC of TDF + 3TC + DTG add another 50mg tablet of DTG to be taken in the evening. This regimen *should be taken until 2 weeks after Tb Rx*.
- For HAART – naïve patients, start ART 2 – 8 weeks after the initiation of TB Rx. For TBM delay up to 8 weeks.

Cont.

- Alternatives if EFV cannot be used: ***Use a (boosted) protease inhibitor/ ritonavir with Rifabutin instead of rifampicin.***
- Alternatives if EFV cannot be used and PI/r not tolerated:
  - AZT + 3TC + ABC/TDF
  - Inferior regimen change to standard ART regimens after Tb Rx is completed
  - Check viral load before change to see if resistance happened when using the inferior regimen.

HIV – HBV coinfection

- TDF + 3TC + DTG or EFV
- Both TDF & 3TC have activity against HBV
- Combination of both drugs prevents HBV resistance

Monitoring Rx - Kenya

- On every visit:
  - Clinical evaluation (Hx & PE)
    - Anthropometry: weight, height, BMI, ADRs
  - TB screening
    - If negative at baseline give **Isoniazid Preventive Therapy (IPT) for 6 months**
  - Always check adherence
  - Pregnancy status: Offer/ monitor FP/ pre – conception counselling

Visit frequency

- Weekly until ART is initiated in about 2 weeks
- After they start,
  - Week 2
  - Week 4
  - Then monthly for 6 months
- If patient is doing well decide on interval, you may see them every 1 – 3 months up to 12 months
- If stable every 3 – 6 months

Cont.

- Hemoglobin
  - Baseline test
  - If patient is on AZT: do at 2 weeks, then at 1 month then at 3 months
  - Then afterwards, it is clinically directed
- CD4
  - Baseline test
  - If treatment failure is detected while monitoring viral load to assess risk of OIs
  - If patient defaults from care (off ART) for at least 6 months

Cont.

- For patients on 2^0 prophylaxis for cryptococcal meningitis (CM).
  - Repeat CD4 every 6 months until CD4 is > 100 cells/mm^3 for 2 consecutive measures 6 months apart and VL undetectable
  - After this CM prophylaxis and CD4 monitoring can be discontinued

Cont.

- Viral load
  - 0 – 24 yrs.: every 6 months
  - > 25 yrs.: 6 months after HAART initiation; Annually thereafter
  - If pregnant & breastfeeding while on HAART regardless of when last VL is done; Every 6 months up to cessation of BF

Cont.

- If VL is undetectable provide enhanced adherence counselling and repeat VL after 3 months whole continue on the regiment the patient was on
- Do VL before substituting single drugs in cases of toxicity

Cont.

- Cervical cancer is a leading cause of cancer death for women in Kenya.
- The risk of developing cervical cancer is greatly reduced with the use of HPV vaccination. Even without the HPV vaccine, morbidity and mortality from cervical cancer can be reduced through early detection with routine screening.
- The national program is moving towards HPV screening as the initial step in cervical cancer risk stratification. ***All HIV positive women should be screened for cervical cancer following the national cervical cancer screening guidelines.***

Drug resistance testing

- Don’t do except
- When treatment failure is confirmed on:
  - A PI based 1st line regimen
  - Failure on 2nd line or subsequent regimens

Table 3.4: Summary of Clinical and Laboratory Monitoring for PLHIV[1]

	Initial Visit	ART preparation	Week (after ART)		Months (after ART)					≥ 12 months
Appointment[2]		Every week[3]	2	4	2	3	4	5	6	Every 1-3 months, depending on stability	Every 3-6 months if stable[4]
History and physical exam[5]	✓	✓	✓	✓	✓	✓	✓	✓	✓	At each visit	At each clinical visit
Adherence assessment and support[6]	✓	✓	✓	✓	✓	✓	✓	✓	✓	At each visit	At each visit
TB Screening	✓	Every visit, using ICF screening tool									
CD4 count	✓	• Baseline, and then only if develops treatment failure (to assess for risk of OIs), or if defaults from care (off ART) for at least 6 months • For patients on secondary prophylaxis for cryptococcal meningitis (CM), repeat CD4 every 6 months until CD4 >100 cells/mm^3 for two consecutive measures 6 months apart and VL undetectable, after which CM prophylaxis and CD4 monitoring can be discontinued • For patients on prophylaxis using dapsone (documented CTX allergy), repeat CD4 every 6 months until CD4 >200 cells/mm^3 for two consecutive measures 6 months apart and VL undetectable, after which dapsone and CD4 monitoring can be discontinued									

HIV Viral Load		• For PCR positive HEIs: baseline at the time of ART initiation • Age 0-24 years: every 6 months • Age ≥ 25 years: at month 6 after ART initiation and month 12 then annually thereafter • For all: before any drug substitution for patients on ART for at least 6 months with no VL results from the last 6 months • For all: after any regimen change (including single drug substitutions), perform VL at months 3 after regimen modification, and then as per population group • For all: any patient with a detectable VL during routine monitoring, follow viral load monitoring algorithm (Figure 6.5)
HIV Viral Load (pregnant/ breastfeeding)		• If on ART at time of confirming pregnancy: VL done at confirmation of pregnancy (regardless of when previously done), then every 6 months until complete cessation of breastfeeding • If starting ART during pregnancy or breastfeeding, VL at 3 months after initiation, and then every 6 months until complete cessation of breastfeeding • For all: any patient with a detectable VL during routine monitoring, follow viral load monitoring algorithm (Figure 6.5)

CrAg	✓	Baseline for adults and adolescents with CD4 ≤ 200 cells/mm^3 (as reflex testing by laboratory), then only if clinical suspicion of CM
Hb	✓	Baseline then symptom directed; if on AZT, baseline then weeks 2, 4, and 12
Pregnancy Status	✓	At every visit for women of reproductive age (by history +/- urine pregnancy test)
Urinalysis (protein & glucose)	✓	Baseline, then annually if on TDF
Creatinine	✓	Baseline, then annually if on TDF
Glucose	✓	Baseline, then annually
Plasma lipid profile	✓	Baseline, then annually
HBsAg	✓	Baseline, followed by immunization for all patients who screen negative (after viral suppression is confirmed)
Syphilis serology (VDRL, TPHA, or RPR)	✓	Baseline, then annually in those at risk and as part of routine ANC profile
Drug Resistance Testing		Not recommended at baseline; DRT recommended once treatment failure confirmed on a PI-based 1st line regimen, or failure on 2nd line or subsequent regimens
ALT		Not recommended for routine baseline or follow-up unless specific clinical indication
Cervical Cancer	All women should be screened for cervical cancer following the national guidelines	
HCV	Baseline for PWIDs or with a history of injection drug use	

Treatment failure

- Clinical failure
  - New or recurrent OI or malignancy after 6 months of ART
    - i.e. new WHO 3 & 4 conditions
  - Confirm with VL
- Clinical and immunological failure not in 2018 guidelines
  - Rely on VL
  - CD4 is not a routine test

Cont.

- Virological failure
  - Persistently detectable or high VL > 1000 copies/ml (even low level viremia)
  - 2 VL measured within a 3 month interval with adherence support between measurements after at least 6 months of using ART
  - For pregnant & BF women, as above but 1 month interval

Causes of Rx failure

- Poor adherence (main cause)
- Pre – existing drug resistance e.g. PMTCT
- Regiments with low potency
- Impaired drug absorption
- Altered pharmacology
  - Drug interactions

Cont.

- Don’t rush to 2nd line therapy
- Multidisciplinary team to discuss reasons for failure
- Improve adherence. If not possible DOT (HCW, families, friends)
- Don’t discontinue a failing regiment until the new regimen becomes available.

2nd line regimens

- AZT + 3TC + ATV/r
- If failing therapy on TDF with HBV coinfection
  - Maintain TDF
  - E.g. TDF/3TC/DTG then switch to TDF/3TC + ATV/r

3rd line regimens

- Consult the regional or national HIV clinical Technical Working Group (TWG).
  - They recommend based on drug resistance testing or drug sensitivity testing.

TOXICITY

- Patients should be informed about possible ADRs before ART initiation (ART & other co – administered drugs)
- Reassure that:
  - ADRs are generally mild & self – limiting
  - Supportive care is available if indicated
  - Rx change may be necessary & will be provided

Cont.

- Alternative explanations for toxicity must be excluded before concluding a reaction is secondary to an ARV.
- Consider
  - A/Es of other drugs
  - Drug interactions
  - Herbal remedies
  - Diseases including OIs
  - IRIS

ADRs

- Graded as (1 – 4)
  1. Mild
  2. Moderate
  3. Severe
  4. Life – threatening
- Check:
  - DAIDs tables
  - Kenya guidelines

1. Mild ADRs

- ***Continue ART***
- Realize that you need to ***support the patient*** as these can affect adherence.
- ***Manage if bothersome***
  - GIT: take with food; If severe → consider anti – emetics
  - CNS: reassure; take at bed time
  - Mild rash: antihistamines

2. Moderate ADRs

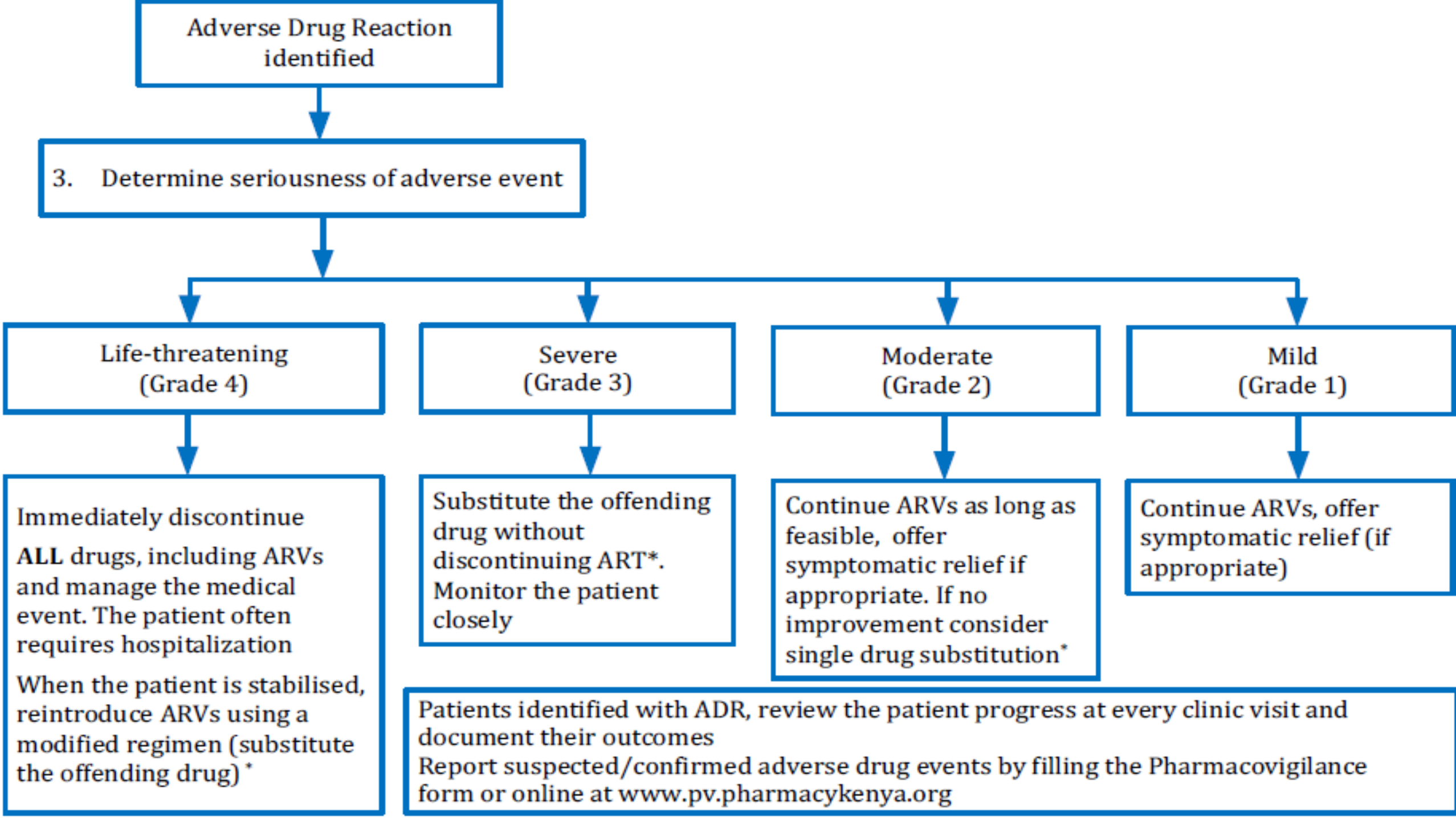
- ***Continue ARVs as long as is feasible***
- Offer symptomatic relief if appropriate
- If no improvement, consider ***a single drug substitution***

3. Severe ADRs

- ***Substitute the offending drug without stopping ART.***

4. Life threatening toxicity

- ***STOP ALL ARVS***
- Patient often requires hospitalization
- Manage ADRs (symptomatic, supportive Rx)
- After resolution: ***substitute single drug with a different toxicity profile***
- Document & tell the patient
- Dose reduction only if plasma level possible


Adverse Drug Reaction identified
3. Determine seriousness of adverse event
Life-threatening (Grade 4)
Severe (Grade 3)
Moderate (Grade 2)
Mild (Grade 1)
Immediately discontinue
ALL drugs, including ARVs and manage the medical event. The patient often requires hospitalization
When the patient is stabilised, reintroduce ARVs using a modified regimen (substitute the offending drug) *
Substitute the offending drug without discontinuing ART*. Monitor the patient closely
Continue ARVs as long as feasible, offer symptomatic relief if appropriate. If no improvement consider single drug substitution*
Continue ARVs, offer symptomatic relief (if appropriate)
Patients identified with ADR, review the patient progress at every clinic visit and document their outcomes
Report suspected/confirmed adverse drug events by filling the Pharmacovigilance form or online at www.pv.pharmacykenya.org

Common toxicities & recommended drug substitution

ARV	COMMON ASSOCIATED TOXICITY	SUGGESTED SUBSTITUTE
TDF	Renal dysfunction If Creatinine Clearance < 50ml/min	Dose adjustment ABC
AZT	Anemia or neutropenia Severe gastric intolerance	TDF
	Lactic acidosis	
EFV	Persistent & severe CNS toxicity/ psychiatric history	ATV/r
DTG	Insomnia	EFV

Common significant ADRs

Table 6.6: Common Significant Adverse Drug Reactions

ARV Agent	Adverse Drug Reaction	High Risk Situations/Comments
NRTIs		
ABC	ABC hypersensitivity reaction (see Table 6.10)	Do not re-challenge
AZT	Anaemia, neutropenia (see Table 6.8)	Risk factors: CD4 count < 200 cells/mm^3; BMI < 18.5 (or body weight < 50 kg); anaemia at baseline; concurrent use of other drugs with similar ADR (cotrimoxazole, gancyclovir, ribavirin)
	Lactic acidosis	Risk factors: Pregnancy; obesity
	Lipoatrophy	Risk factors: Low CD4 count
TDF	Renal dysfunction (see Figure 6.4)	Risk factors: Underlying renal disease; age > 40 years; BMI < 18.5 (or body weight < 50 kg); diabetes; hypertension; concomitant PI use or nephrotoxic drug

NNRTIs		
All NNRTIs	Rash/hypersensitivity (NVP>>EFV>ETR)	Risk factors: for NVP hypersensitivity, women with CD4 count > 250 cells/mm^3, men with CD4 count > 400 cells/mm^3 Manage rash as per Table 4.4
EFV	CNS side-effects	Risk factors: Pre-existing psychiatric disorder
	Gynaecomastia	Switch from EFV to an alternative, and consult if gynecomastia does not improve
NVP	Hepatotoxicity (see Table 6.9)	Risk factors: HBV or HCV co-infection; concomitant use of hepatotoxic drugs; women with CD4 count > 250 cells/ mm^3; men with CD4 count > 400 cells/mm^3

PIs		
All PIs boosted with RTV	GI intolerance (LPV/r>DRV/r>ATV/r)	Consult
	Dyslipidaemia (LPV/r>DRV/r>ATV/r)	Risk factors: Obesity; sedentary lifestyle; diet high in saturated fats and cholesterol
ATV/r	Hyperbilirubinemia	This only requires drug substitution if cosmetic effect of jaundice is likely to interfere with patient adherence
DRV/r	Rash/hypersensitivity	Risk factors: sulfa allergy
INSTIs		
DTG	Insomnia	Give in the morning; if no improvement then try giving with low fat meal or on empty stomach
All INSTIs	Rash/hypersensitivity	Consult

Cont.

- Do a VL before a single drug substitution if treatment has been ongoing for > 6 months.
  - If undetectable, substitute one drug then check VL after 3 months
  - If Rx failure
    - Enhanced adherence counselling
    - Consider ARV Hx, drug interactions, resistance tests
    - Change to 2nd line.

Cont.

- ADRs can be precipitated or exacerbated by:
  - Concomitant drugs with similar toxicity
  - Comorbidity
  - Other D/Is
  - Genetic factors
- Establish if ADR is due to ART or other cause

Anemia

- Associated ARV: **AZT**
- Onset: variable, weeks to months
- Presentation
  - Asymptomatic or mild fatigue, pallor, tachypnea
  - Rarely CCF

Cont.

- Risk factors of developing anemia:
  - Hemoglobinopathy e.g. SCD
  - Poorly controlled HIV
  - Marrow toxic drugs (TMP – SMX, Rifabutin
  - Iron deficiency
- Prevention: avoid AZT in anemic patients

Management of anemia

- Discontinue marrow toxic drugs if feasible (depending on grade of anemia).
- Treat co – existing causes of anemia: iron deficiency, O/Is, malignancies
- Rarely necessary to discontinue ARV therapy
- For persistent anemia thought to be associated with ZDV
  - Change ZDV to TDF
  - Consider hematinics, EPO

Kenyan guidelines

- If Hb > 9.5g/dL one may start AZT
- If on AZT & one develops grade 2, 3 or 4 anemia
  - Stop AZT & change to TDF
  - Give hematinics
  - Transfuse if indicated

Grading

Grade	Hemoglobin (g/dL)	Neutrophil count
1	8.5 – 9.4	1000 – 1300
2	7.5 – 8.4	750 – 999
3	6.5 – 7.4	500 – 749
4	< 6.4	< 499

TDF A/Es

- Renal insufficiency, Fanconi syndrome, proximal tubulopathy
- Osteomalacia
- Severe acute exacerbation of hepatitis may occur in HBV co – infected patients who discontinue TDF
- Asthenia, headache, N, V, D & Flatulence

Renal dysfunction

- Associated ARV: TDF
- Onset: weeks to months after initiation of therapy
- Clinical manifestations – common
  - ↑ serum creatinine
  - Proteinuria
  - Hypophosphatemia
    - Usually asymptomatic
    - May present with bone & muscle pain, weakness

Cont.

- Risk factors
  - Pre – existing renal dysfunction
  - Risk ↑ with longer duration of TDF treatment
- Prevention & monitoring
  - Urinalysis for protein & glucose every 6 months
  - Serum creatinine every 6 months
  - Serum phosphate if persistent proteinuria, glycosuria or bone pain & muscle weakness

Cont.

- Toxicity ↑ with duration of TDF treatment, ∴:
  - Frequency of monitoring should not ↓ with time
  - Abnormal values should be confirmed by a repeat test to ensure that the drug is being changed based on correct values.
- Management
  - Consider using another ARV drug e.g. ABC
  - Doses can also be adjusted for renal impairment
    - May not be prudent because of difficulty of distinguishing the effects of TDF vs. primary renal disease

3TC A/Es

- Minimal toxicity
- Severe acute exacerbation of hepatitis may occur in HBV coinfected patients who discontinue 3TC

EFV A/Es

- Rash
- Neuropsychiatric symptoms
- ↑ transaminase levels
- Hyperlipidemia
- Teratogenic in non – human primates & potentially teratogenic in humans

Neuropsychiatric symptoms

- Associated ARV: EFV
- Onset
  - 1 – 2 days after initiating treatment
  - Most symptoms subside or diminish by 2 – 4 weeks
  - May persist in a minority of patients

Clinical manifestations of neuropsychiatric symptoms

- Dizziness
- Somnolence
- Insomnia
- Abnormal dreams
- Impaired concentration
- Psychosis
- Suicidal ideation
- Seizures (including absence seizures)

Cont.

- Risk factors
  - Insomnia is associated with ↑ EFV → concentration of ≥ $4\mu g$
  - Presence of CYP450 polymorphisms that ↓ EFV metabolism
  - Prior history of psychiatric illness or use of psychoactive drugs

Cont.

- Prevention
  - Administer EFV on an empty stomach preferably at bedtime
    - Fatty meals ↑ peak concentration; hence avoid them;
      - These meal requirements are only for the initial weeks when CNS A/Es are common
  - Use with caution in the presence of psychiatric illness or with concomitant use of psychoactive drugs

Cont.

- Management
  - Reassure that symptoms subside for most patients
  - Consider EFV trough levels if symptoms are excessive or persistent
    - If high, consider dose reduction or drug substitution

Nausea & vomiting

- Associated with any ARV drug but mainly seen with: ***ZDV & PIs*** e.g. LPV/r
- Onset: early
- Prevention & monitoring
  - Take PI with food
  - Generally improves with time
  - Monitor for weight loss, dehydration & ARV adherence
    - If patient vomits within 30 minutes, repeat the dose.

Cont.

- Management
  - Reassure that symptoms will likely decrease over time
  - Antiemetics in extreme or persistent cases.

Diarrhea

- Associated ARV: ***PIs***
- Onset/ clinical manifestations
  - Early
  - Generally soft, not watery & more frequent stools
- Prevention & monitoring
  - Generally improves with time (usually 6 – 8 weeks)
  - Monitor for weight loss & dehydration

Cont.

- Management
  - Exclude infectious causes of diarrhea
  - Bulk – forming agents: psyllium
  - Antimotility agents: loperamide

NVP A/Es

- Rash, including SJS
- Symptomatic hepatitis
  - Higher frequency in ARV – naïve patients
  - Female patients with pre – NVP CD4 counts > 250 cells/ mm^3
  - Male patients with pre – NVP CD4 counts > 400 cells/mm^3
  - NVP should not be initiated in these patients unless the benefit clearly outweighs the risk

Hepatotoxicity

- Associated with all ARVs but the most likely ones are ***NVP & Tipranavir***
- Onset: Hepatitis generally occurs within the first few months of therapy but may occur later
- Clinical manifestations
  - Asymptomatic elevation of AST & ALT
  - Symptomatic hepatitis: nausea, fatigue, jaundice
- Prevention: Avoid concomitant use of hepatotoxic medications e.g. anti – TB drugs

Management of drug related hepatotoxicity

- ALT
  - If < 2.5 times the ULN: retain regimen, repeat test in 2 weeks
  - If 2.5 – 5 times the ULN: retain regimen, repeat test in 1 week
  - If > 5 times the ULN: discontinue offending drug
- If a symptomatic hepatic event occurs on NVP permanently discontinue NVP.
- Consider viral causes of hepatitis: HAV, HBV, HCV, EBV & CMV

Skin rash

- All ARVs esp. ***NVP, ABC, Cotrimoxazole (CTX), EFV***
- Occurs in the 1st 2 – 4 weeks
- More common in *females* & those *allergic to Sulphur drugs*

Steven Johnson Syndrome (SJS), Erythema Multiforme (EM), Toxic Epidermal Necrolysis (TEN)

- Many ARVs
- MC: NVP, EFV, ETR

Clinical grading of ARV associated rash

Rash	
Grade 1	Erythema, pruritus affecting <50% BSA
Grade 2	Diffuse maculopapular rash OR dry desquamation affecting >50% of BSA
Grade 3	Vesiculation OR moist desquamation OR ulceration
Grade 4	Mucus membrane involvement; SJS, EM

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Table 4.4: Management of Drug-Associated Skin Rash

Severity	Characteristics	Action
Mild	Dry; erythema +/- fine papules; pruritus; affecting < 50% of body surface area	Continue CTX; close monitoring; symptomatic treatment with antihistamines +/- topical steroids (NOT oral steroids)
Moderate	Dry; erythema +/- fine papules; pruritus; affecting ≥ 50% of body surface area	Stop CTX; symptomatic treatment with antihistamines +/- topical steroids (NOT oral steroids); trial of desensitization after symptoms completely resolved
Severe	Mucosal involvement; blistering; associated fever; any % of body surface area	Stop CTX; admission to hospital for supportive management (IV fluids, wound care, pain control, infection control, monitoring for super-infection); **patient should NEVER be re-challenged with CTX or other sulfa-containing drugs;** document and report adverse event and issue patient alert card

Systemic hypersensitivity reaction ± skin manifestation

- Associated ARV: ***ABC***
  - Screen for HLA*B5701
- Also seen in ***NVP, DTG***

ABC hypersensitivity

- Diagnosis
  - Within 8 weeks of initiating an ABC – containing regimen
  - Any 2 of the following symptom groups concurrently
    - Fever
    - Erythematous &/ or pruritic rash
    - Respiratory symptoms: SOB &/or sore throat &/or cough
    - GI symptoms: Nausea &/or Vomiting &/or Diarrhea
    - Extreme fatigue &/or body pain preventing normal activities
  - When there is not a more likely alternative explanation for the symptoms

Management

- Stop ABC immediately & substitute with an alternative ARV
- Patient must never be re – challenged with ABC – a single dose could result in a fatal hypersensitivity
- Reaction: issue an alert card
- Clearly mark file and educate patient about avoiding ABC in future

Cont.

- ABC hypersensitivity reaction is rare in our population always consider other more likely possible diagnoses.
- Symptoms generally get worse within hours after each dose of ABC & this should alert you to a possible ABC hypersensitivity

DTG A/Es

- Onset day: 7 – 30 for CND
- Insomnia: Take in the morning; On empty stomach or low fat meal
- Headache
- Neuropsychiatric symptoms
  - Depression &/or suicidal thoughts or actions
  - Esp. if history of psychiatric illness
- Nausea & vomiting: resolves in 1 – 2 weeks.

Cont.

- Hypersensitivity reactions
  - Rash
  - Constitutional symptoms
  - Organ dysfunction: including liver injury

NOTE

All suspected/ confirmed Adverse Drug Reactions should be reported to the Pharmacy & Poisons Board by filling the Pharmacovigilance form or online at www.pv.pharmacykenya.org .

References

- Guidelines on use of Antiretroviral Drugs for Treating & Preventing HIV in Kenya 2018 Edition.
- Medical management of HIV infection, Kenya edition 2003
- AIDs info
  - Guidelines for the use of antiretroviral agents in HIV – 1 infected adults and adolescents
  - Guidelines for the use of antiretroviral agents in pediatric HIV infection

3. TREATMENT OF OPPORTUNISTIC INFECTIONS IN HIV

BY: DR. OMONGE

TYPED BY NAILA KAMADI

Common OIs

- Tuberculosis - Hx , S/S, Dx, Rx
- Cryptococcal meningitis
- Pneumocytis Jerivocii
- Toxoplasmosis
- Cytomegalovirus
- Non-infectious - KS , lymphoma , cacx

Figure 1.1 Natural History of HIV Infection: CD4 Decline and Opportunistic Infections

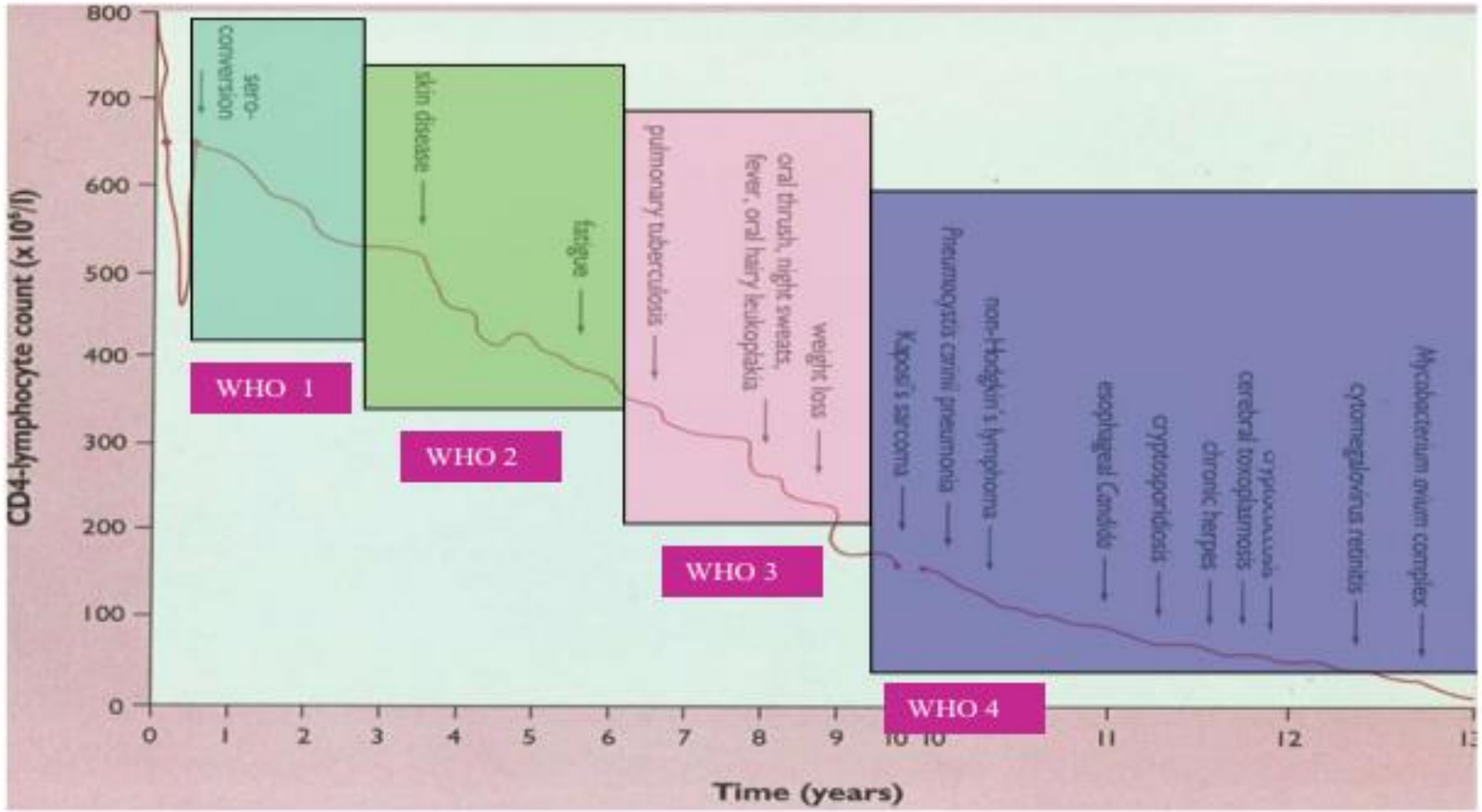


Table 1.1: CD4 and Risk of Opportunistic Infections and Conditions

CD4 Count (cells/mm^3)	Likely Opportunistic Infections and Conditions
Any CD4	HIVAN, KS, TB
> 200	Bacterial pneumonia, TB, sensory polyneuropathy, HAD, PPE, thrush, EPTB
100- 200	Above plus PCP, EPTB
< 100	Above plus Toxoplasmosis, PML, NHL. Cryptococcal meningitis
< 50	Above plus MAC, CMV retinitis, , primary CNS lymphoma

HIVAN = HIV associated nephropathy; KS = Kaposi's Sarcoma; PPE = Papular Pruritic Eruptions; HAD = HIV associated dementia; EPTB = Extrapulmonary TB; PML = Progressive multifocal encephalopathy; NHL = Non-Hodgkin's Lymphoma;

MAC = Mycobacterium Avium Complex; CMV = Cytomegalovirus

Cotrimoxazole Desensitization

Table 1.2: Standard Desensitization Regimen (Days)

Day	Dose of TMP/SMX Suspension 40/200 per 5ml
1	0.5ml
2	1ml
3	2ml
4	3ml
5	4ml
6	5ml
7	1 SS tablet
8	2 SS tablets/1 DS tablet per day

Table 1.3: Rapid Desensitization Regimen (Hours)

Hour	Dose of TMP/SMX 40/200 per 5ml
0	0.5ml
1	1ml
2	2ml
3	3ml
4	4ml
5	5ml
6	1 SS tablet

Isoniazid preventive therapy(IPT)

- The risk of new tuberculosis disease in HIV-infected individuals can be lowered, but not eliminated, by reducing exposure to TB, using isoniazid preventive therapy (IPT), and ART.
- INH given for a 6–9 month period reduces incidence of TB by about 60% in PLHA with a positive tuberculin skin test, and by about 40%, when used irrespective of skin-test results.
- Some centres may already be offering IPT routinely to PLHA. **Where IPT is used, it is important that screening for TB is done diligently, adherence counselling is provided and active patient follow-up is possible in the case of defaulters.**
- Where IPT is **NOT** used routinely in PLHA, it **should be offered to all children under 5 years exposed to "open TB" in a close contact** *after* active TB has been excluded.
- *Consideration should also be given to IPT provision in all HIV infected children after exclusion of TB because of the proven benefits.*

Table 1.6: Clinical Presentation of IRIS

Responsible Condition	Clinical Presentation of IRIS
TB	IRIS presents from 1-6 wks after starting ART. Commonly high fever, cough, dyspnoea; new or increased lymphadenopathy (peripheral or mediastinal); lymph node abscesses; worsening of pulmonary disease with new or increased infiltrates or effusion; new or worsening CNS presentation; other new extrapulmonary lesions
Herpes Zoster	Within the first 4 months of ART. Presents with herpes zoster,
Cryptococcus	Presents 1 wk to 11 months after ART initiation. Fever, worsening headache, lymphadenitis, new or worsening signs of meningitis; pulmonary disease; skin lesions,
PCP	Fever, cough, dyspnoea in patients on treatment, those recently treated or those undiagnosed. CXR may show worsening radiographic picture
Skin	New or worsening PPE, eosinophilic folliculitis, new presentation or chronic mucocutaneous herpes lesions
Malignancies	New or worsening KS lesions
Hepatitis B	Worsening hepatitis, confirmed by rising ALT AST. Can present late, up to 9 months after ART initiation. "May be associated with re-appearance of positive HBSAG and HBeAG in patients previously positive HBc Ab/HBsAb"

Treatment

No single treatment option exists for IRIS and management depends on the underlying condition, as well

Pr

Table 3.5: Summary of PCP Treatment

	Drugs	Dose
1st Line	Cotrimoxazole (Single strength, SS 400/80; double strength, DS 800/160) given for 21 days	20mg/kg of the trimethoprim component. (Alternatively, weight divided by 4 gives the number of SS tablets per 24 hr period)
2nd Line	Clindamycin *plus* Primaquine Pentamidine Given for 21 days	Clindamycin 600-900mg 8 hourly *plus* Primaquine 15-30mg/day Pentamidine 4mg/kg/day IV/IM
For the severely ill (O_2 saturation on air < 90%)	Add prednisolone from first day of treatment	40mg BD for 5 days, then 40mg daily for 5 days, then 20mg daily for the remaining 11 days

Table 4.1. Summary: HIV Associated Oral Lesions

Clinical condition	Presentation	Management
Candidiasis	White curd like patches on the tongue and inner surface of cheeks; can be easily scraped off revealing redness underneath. May also present as shiny erythematous patches or angular cheilitis	Nyastatin mouth drops 500000 units (5 ml) 4x per day for 7-14 days Miconazole gum patch **Systemic therapy if above fails:** Fluconazole 100 mg/day for 7 days Itraconazole 200mg/ day for 7 days (swished in mouth and swallowed on an empty stomach)
Apthous Ulcers	Ulcers in the mouth that are painful, are well defined with elevated margin and whitish floor	Antiseptic mouth washes (e.g. difflam) Local anaesthetic preparation prior to meals Corticosteroid preparations in oral gel 2° infection of ulcers is common requiring metronidazole + penicillin OR co-amoxiclav **For refractory cases:** Oral prednisolone (40mg per day for1-2 weeks before tapering) Dapsone 100mg /day **Resolves with ART.**

Table 4.1. Summary: HIV Associated Oral Lesions cont.

Clinical condition	Presentation	Management
Kaposi's Sarcoma	Lesions usually found on the roof of mouth or gums and do not hurt or itch; vary in colour from dark red, purple to brown. They start as patches then progress to thick bumps, to may become large tumours.	ART together with specific treatment of KS. Should be managed by an experienced clinician.
Oral Hairy Leukoplakia	Oral mucosal disease, associated with EBV, non-painful white plaque along the lateral tongue borders. Diagnosis is clinical.	Treatment not required.
HSV - 1	Painful, progressive anogenital or orolabial ulceration; More likely to recur or persist in PLHA	Aciclovir 400mg 8 hourly for 7-10 days

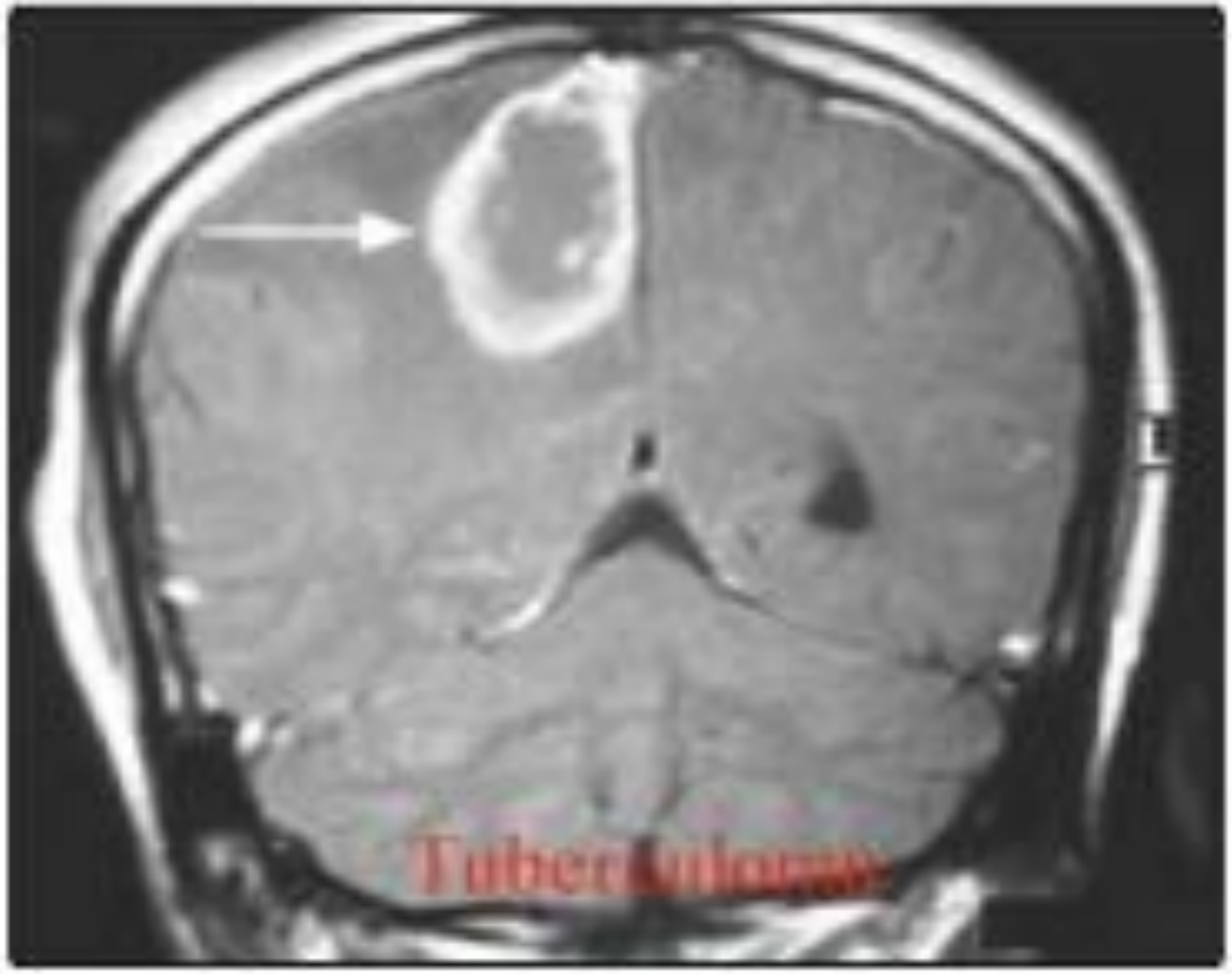
Table 4.2: Summary: Treatment of Oesophagitis in PLHA

Cause	Treatment
Oesophageal Candidiasis	**Preferred**: Fluconazole 200mg stat then 100mg OD PO x 14-21 days. IV if patient cannot swallow **Failure to improve on Fluconazole**: Increase dose to 400-800mg/day OR Itraconazole *solution* 200mg PO x 14-21 days OR Amphotericin B IV 0.3-0.7 mg/kg/day x 14-21 days If no response consider anti-HSV treatment
Herpes Simplex Virus (HSV) Oesophagitis	Aciclovir 800mg 6 hourly x 14-21 days Or Valaciclovir 1g PO TDS x 14-21 days
CMV Oesophagitis	Valganciclovir 900mg BD x 3 weeks
Aphthous Ulcers	Prednisolone 40mg/day x 7-14 days, then taper

Table 4.3: Summary: Causes of Diarrhoea

Cause	Acute Diarrhoea	Chronic Diarrhoea
Bacterial Infections (watery diarrhoea, bloody, fever)	Non-typhi *Salmonella* species (NTS), *Shigella*, *Campylobacter jejuni*, *Yersinia enterocolitica*, *Escherichia coli* and *Vibrio cholera*, shigella, *Clostridium difficile*, *Vibrio cholera;* **Food borne toxigenic diarrhoea** (staph aureus, B cereus)	Salmonella typhi; Mycobacteria avium complex, mycobacterium TB
Protozoal Infections (watery diarrhoea, bloating, flatulence)	*Giardia lamblia*, *Entamoeba coli*	Cryptosporidium, *Giardia lamblia*, *Isospora belli*, Ent. histolytica, microsporidia
Parasitic		Strongyloides stercoralis
Viruses	Enteric viruses	CMV
Medication	Antibiotics, ARV drugs – PIs, DDI	ARVs
Toxins	Clostridium difficile, staph aureus, bacillus cereus	
Malignancies		Lymphoma, endocrine tumours
Other	Ischemic colitis	Endocrine disorders, malabsorption, ulcerative colitis, radiation or chemotherapy, unknown

Tuberculoma



Treatment of Toxoplasmosis

The Preferred regimen:

Pyrimethamine 200 mg loading dose, then 50 mg –75 mg/day

+

Sulfadiazine 1000 mg to 1500mg P.O. 6 hourly

+

Folinic acid (leucovorin) 10-20mg/day PO

Folate is not a substitute for Folinic acid. The dose of Folinic acid can be increased to >50 mg/day to reduce Pyrimethamine-associated haematological toxicity

Alternative regimen:

Cotrimoxazole: 5mg/kg of Trimethoprim or 25mg/kg of CTX BD per day for 6 weeks (e.g. for 60kg man, 4 SS tablets per day). This is the regimen of first choice locally in the absence of key constituents of the preferred choice above. An advantage of this regimen over the above one is that it can also be given IV in patients unable to take oral treatment.

Progress

Clinical improvement is usually expected within 1 week and improvement demonstrated by CT scan or

Cryptococcal meningitis

Preferred Treatment Regimen (See Appendix H for protocols)

- **Induction**: initial treatment is with Amphotericin B (0.7 - 1.0 mg/kg/d) for 2 weeks or until the patient is clinically stable. Amphotericin B therapy should be administered in qualified health facilities capable of close clinical and laboratory patient monitoring. In facilities incapable of administering Amphotericin B sole, treatment with Fluconazole (400-800 mg/d for 12 weeks) may be an alternative, although treatment failure and mortality are high.
- **Consolidation** phase: Fluconazole 400-800 mg/d for 8 weeks; the higher dose must be used in patients on concomitant rifampicin
- **Maintenance**/suppressive phase: Fluconazole 200 mg/d
- **Discontinuation of Fluconazole**: Fluconazole can be stopped in patients who have been on ART and have documented immune reconstitution as shown by CD4 consistently above 100 cells/mm^3 for at least 6 months.

Alternative Treatment Regimen

- Induction: Fluconazole 400-800 mg per day for 2 weeks

Review the other opportunistic diseases

Your naked body (what they see) deserves the honor of being shared only with someone who is covenanted to never stop loving your naked soul (who you truly are).

Abstinence, **in the long run**, is the most pleasurable sex position.

#Jesus_Christ_Our_Wisdom☺

10. DERMATOLOGIC THERAPEUTICS LEVEL VI MBCHB 7TH/5/2019

BY: DR. A. INDALO

Introduction

- The integument or skin is the largest organ f the body making up 16% if body weight with a surface area of about $18m^2$
- There are 3 structural layers:
  - Epidermis
  - Dermis
  - Subcutaneous layer

Functions of skin

- Mechanical/ physical barrier
- Temperature regulation
- Water conservation
- Microbiological protection
- Radiation protection
- Sensation
- Immune responses
- Synthesis
- Storage
- Psychosocial

Skin/ dermatological preparations

- Medications for treatment of skin disorders can be delivered by:
  - Topical
  - Systemic
  - Intra – lesional
- Topical or systemic routes can be combined with phototherapy to treat certain skin conditions such as ***psoriasis***.

Cont.

- Dermatological preparations are intended to act locally in the treatment of skin disorders.
- It is desirable for systemic absorption not to occur but this does happen.

Examples

- 5 – FU, that can be used for the treatment of skin pre-malignant & malignant lesions, minimizes its systemic exposure & it has serious adverse effects
- Systemic glucocorticoids give good anti – inflammatory response but their adverse effects are considerable.

There are 3 potential skin penetration routes to the viable tissue

1. Through the hair follicles with their associated sebaceous glands
2. Via the sweat ducts
3. Across the stratum corneum between these appendages.

Stratum Corneum (SC)

- Thin, tough, relatively impermeable membrane that usually provides the RLS in percutaneous absorption.
- The entire horny layer provides the diffusional resistance.
- The membrane allows no drug to pass through readily but nearly al drugs do penetrate to some extent.

Variables determining the pharmacologic response to drugs applied to skin

1. Regional variation in drug penetration
2. Concentration gradient
3. Dosing schedule
4. Chemical form of the drug, vehicles and occlusion
5. Aging and environmental factors

1. Regional variation in drug penetration

- Scrotum, face, axilla and scalp are more permeable than the forearm and may require less drug for equivalent effect
- Absorption is also rapid in regions with large, numerous hair follicles
- Absorption is decreased in areas of skinned with thickened stratum corneum e.g. foot
- On the other hand absorption from the palm which has a fairly thick SC and no hair follicles is comparable to that of the forearm.

2. Concentration gradient

- Increasing the concentration gradient will increase the mass of drug transferred per unit time just as diffusion across other barriers.

3. Dosing schedule

- Dosing schedule
  - Because the skin’s physical properties, it acts as a reservoir for many drugs.
  - As a result, the local half life may be long enough to permit once or twice daily application of drugs with short systemic half lives.

4. Chemical form of the drug: vehicles & occlusion

- Vehicles may have drying or moisturizing effects and may themselves have therapeutic effects.
- Hydration of the skin alters the barrier characteristics and promotes absorption e.g. occlusion is effective in maximizing absorption of many drugs.

Cont.

- An appropriate vehicle will maximize the ability of the drug to penetrate the outer layers of the skin.
- Penetration enhancers produce structural changes in the skin & promote absorption e.g. ***dimethyl sulfoxide, propylene glycol, urea***

5. Aging & environmental factors

- These lead to dehydration of the skin can retard absorption.
- Environmental temperature can affect hydration of the SC as well as local blood flow.
- Damage of the SC promotes absorption of drugs through the skin.
  - Do not apply keratolytic agents e.g. salicylic acid on damaged skin.

NB

- Ideal bioavailability is confusing → we wish to have maximum penetration of drug into skin yet we wish to minimize systemic absorption to avoid A/Es – this delicate balance is not always achieved.

Cont.

- Systemic toxicity of drugs applied locally are of particular concern in infants because they appear to absorb drugs through skin as efficiently as for adults and the ratio of SA:BWT in the new born is 3 times that in adults.
- Hydrocortisone cream is given to infants.

Complications of local treatment

- ***Absorption***: Corticosteroids, salicylic acid, gamma benzene hexa – chloride → ***systemic toxicity***
- ***Sensitization***: Lanolin, Antibiotics, LAs, local antihistamines
- ***Irritation***: dithranol, podophyllin, urea
- ***Inevitable local toxicity***: eusol (damage to regenerate tissue), corticosteroids (striae)
- ***Inappropriate use***: corticosteroids on fungal infection, crotamiton on eczema→ irritation

Dermatologic formulations classification depending on the vehicle base

- Tinctures
- Wet dressings
- Lotions
- Gels
- Aerosols
- Powder
- Pastes
- Creams
- Ointments

In order of increasing ability of the vehicle to retard evaporation from the skin, i.e., least with tinctures and wet dressings and greatest with ointments

Newer vehicles: liposomes and micro particles

- Micro particles
  - Polymer based microstructures in which drugs can be trapped
  - Allow for metered drugs release
  - Cause less irritation
- Liposomes
  - Most readily penetrate compromised epidermal barriers.
  - Initially remain in liquid state and absorption is slow; in the 2nd stage the preparation dries & intercalates in the lipids of skin surface & diffuses in the SC

Choice of formulation

- Depends on the condition being treated.
- Acute inflammation with oozing, vesiculation & crusting is best treated with drying preparations such as tinctures, wet dressings and lotions.
- Chronic inflammation with xerosis, scaling & lichenification is best treated with more lubricating preparations such as creams and ointments.
- For scalp & hairy areas, tinctures, lotions, gels and aerosols are convenient.

NB

- Give enough medication for the period of treatment.
- Approximately 15 – 25g covers adult body if thin film of cream is used.
- Give warning to the patient e.g. how to wash out drug from skin.

Skin preparations

- Antibacterial agents
- Antifungals: topical, oral
- Antiviral agents
- Ectoparasiticides
- Agents affecting pigmentation
- Sunscreens and camouflages
- Acne preparations
- Anti – inflammatory agents
- Keratolytic and destructive agents
- Trichogenic agents
- Miscellaneous oral medications

Topical corticosteroids

- Used for treatment of inflammatory conditions other than those due to the infection.
- They are not curative but they suppress various components of the inflammatory reaction.
- Rebound exacerbation of the condition may occur if treatment is discontinued.
- Absorption is greatest from areas of ***thin skin, raw surfaces, intertriginous areas*** & is ***increased by occlusion.***

Cont.

- Formulations include: ***ointments, lotions, creams***
- Produce dramatic suppression of ***skin diseases in which inflammation is a prominent feature*** e.g. eczema, infantile eczema, atopic dermatitis, dermatitis herpetiformis, contact dermatitis, dermatitis venenata, seborrhoeic dermatitis, neurodermatitis & psoriasis.

Cont.

- Intra – lesional injection of corticosteroids can sometimes hasten the resolution of ***chronic skin lesions such as lichen planus, lichen simplex, keloids and sarcoidosis of the skin***.
- In such cases the corticosteroid is sometimes injected with LA into the lesion & for this purpose ***fluorinated compounds (more potent)*** are usually preferred.

Topical preparations

- Hydrocortisone esters: butyrate, valerate
- Betamethasone esters: valerate, dipropionate
- Clobetasone esters: propionate, butyrate
- Desoxymethasone
- Diflucortolone acetonide
- Triamcinolone
- Amcinolone etc.

Local side effects

- Spread & worsening of untreated infection.
- Thinning of the skin: may be restored over a period of time although original structure may never return.
- Irreversible striae atrophicae
- Increased hair growth
- Perioral dermatitis, an inflammatory pimple.

Cont.

- Acne at the site of application in some patients
- Mild depigmentation & vellus hair
- Children esp. babies are particularly susceptible to the side effects therefore use mild corticosteroids such as hydrocortisone.

Topical antibacterial preparations

- Bacitracin & gramicidin
- Polymyxins: polymyxin B sulphate, colistin (polymyxin E)
- Mupirocin
- Neomycin & gentamicin
- Fusidic acid
- Silver sulphadiazine
- Framycetin sulphate gauze dressing
- Tetracyclines
- Metronidazole
- Clindamycin
- Erythromycin

Topical antibacterials may be useful in:

- Preventing infection in clean wounds
- Reducing colonization of nostrils (nares) by *S. aureus*
- Axillary deodorization
- Management of acne vulgaris
- Some preparations contain steroids & they may be useful in the treatment of ***diaper dermatitis, otitis externa & impetiginized eczema***.

Cont.

- Selection depends upon diagnosis & if possible M/C/S results.
- Pre – packaged antibiotic preparations contain fixed dosage(s) well above the therapeutic threshold.
- The formulations offer the advantages of:
  - Efficacy
  - Broader coverage for infections due to undetermined pathogens
  - Delayed microbial resistance to any single component antibiotic.

Cont.

- For some infections e.g. erysipelas & cellulitis systemic antibacterials is the method of choice → the infections are too deeply rooted for adequate penetration of topical preparations.

BACITRACIN & GRAMICIDIN

- Active against G+ve organisms e.g. strep, pneumococci & staph; anaerobic cocci, neiseriae, tetanus bacilli and diptheria bacilli.
- Bacitracin is compounded alone or in combination with neomycin and/or polymyxin B

- **Bacitracin is poorly absorbed from the skin & so systemic toxicity is rare**
- **Gramicidin is available for topical use in combination with:- neomycin, polymyxin-B, bacitracin and nystatin. Systemic toxicity limits its use**

MUPIRICIN (PSEUDOMONIC ACID)

- Effective against most G+ve aerobic bacteria including methicillin-resistant Staph. Aureus
- Effective in Tx of localised impetigo
- Activity enhanced by acidic skin pH

POLYMYXIN-B SULPHATE

- Polymyxins are polypeptide antibiotics
- Are like cationic agents
- Attach & disrupt bacterial cell membranes
- Also bind to and inactivate endotoxins
- Effective against G-ve organisms including Ps. Aeroginosa, E. coli, Enterobacter and Klebsiella
- Most strains of Proteus and G+ve organisms are resistant

- Available in combination with various antibiotics
- Poor absn from skin but may be absorbed from denuded skin or open wounds to cause neuro- and nephrotoxicity
- Colistin (Polymyxin E) may be given parenterally for Tx of resistant strains of Ps. Aeroginosa & Acinetobacter baumannii

NEOMYCIN & GENTAMICIN

- Aminoglycoside antibiotics active against G-ve organisms including E. coli, Proteus, Klebsiella and Enterobacter
- Neomycin available alone or in combination with polmyxin, bacitracin, and other antibiotics, & also with amino acids (cystine & glycine)

- Topical neomycin rarely gets absorbed BUT gentamicin in water miscible prep applied on large areas of denuded skin (i.e. burns) will appear in sufficient []s in plasma
- Both drugs will accumulate in renal failure with subsequent nephro, neuro and ototoxicity
- Sensitization may occur with neomycin & there is cross-sensitivity with other aminoglycosides

FRAMYCETIN SULPHATE gauze dressing:

- **Effective against a wide range of organisms**
- **Oint of framycetin & gramicidin available for superficial bacterial infections**

FUSIDIC ACID:

- **Effective against staph, strep, Corynebacteria, neiseria, certain clostridia and Bacteroides**
- **Also comes in combination with steroids such as betamethasone**

SILVER SULPHADIAZINE

Principally indicated:

- **For prophylaxis and Tx of infection in burn wounds**
- **As an adjuvant to short term Tx of infection in leg ulcers and pressure sores**
- **As an adjuvant to prophylaxis in skin graft donor sites and extensive abrasions**
- **For conservative Mx of finger-tip injuries**

NB: Contraindications as for sulphonamides

VIRAL INFECTIONS

- Verrucae (human papilloma virus or HPV)
- Condyloma acuminatum (HPV)
- Herpes simplex (HSV)
- Molluscum contagiosum (pox virus)
- Varicella (chicken pox)
- etc

ANTIVIRAL PREPARATIONS

- **ACYLOVIR:-**

  - Cream for Tx of initial & recurrent labial and genital herpes simplex infections – begin Tx as early as possible

  - Systemic Tx necessary for buccal or vaginal infections or if cold sores recur frequently

  - Herpes zoster also requires systemic Tx

- **FAMCYCLOVIR & VALACYCLOVIR are esters of acyclovir used systemically to treat herpes simplex and varicella infections**
- **PENCYCLOVIR Cream for Tx of mucocutaneous (e.g. labial) herpes simplex infection**
- **PODOPHYLLIN & PODOFLOX for Tx of moist watts of condyloma**

IMIQUIMOD:

- Immune response modifier which induces interferon production
- Tx of condyloma & is efficacious for Tx of verrucae, molluscum contagiosum and superficial basal cell carcinoma.

TOPICAL ANTIFUNGALS

- **FOR DERMATOPHYTOSES**

  - Imidazole antifungals – clotrimazole, econazole, ketoconazole, miconazole, and sulconazole

  - Terbinafine, amorolfine, undecenoates, compound benzoic acid oint (Whitefield's oint), tolnaftate (for athlete's foot)

- Tinea infection of the nails – amorolfine and tioconazole but mostly systemic Tx

- **PITYRIASIS VESICOLOR**

  - Ketoconazole shampoo; selenium sulphide shampoo use as lotion[{diluted with water to reduce irritation] & left for at least 30 mins or overnight ; it is applied 2-7 times over a fortnight and the course repeated if necessary

  - Topical imidazoles and terbinafine are altenatives or systemic azole antifungal

FOR CANDIDIASIS:-

- Topical imidazole antifungals- clotrimazole, econazole, ketoconazole, miconazole & sulconazole; terbinafine
- Refractory candidiasis requires systemic Tx e.g. with a triazole such as fluconazole

11. GERIATRIC THERAPEUTICS
LEVEL VI MBCHB
14TH/ 6/ 2019

BY: DR. INDALO

TYPED BY NAILA KAMADI

- Introduction
- Pharmacokinetics in the elderly
- Pharmacodynamics in the elderly
- Adverse drug events
- Drug-Drug interactions
- Drug-Disease interactions
- Guidelines in Rx of the elderly
- Conclusion

INTRODUCTION

- Geriatric medicine is the branch of medicine concerned with the clinical, preventive, remedial and social aspects of illness in the elderly.
- Unfitness could be due to disease, chronic alcoholism, social problems e.g. living alone
- Ageing/disease/social problems/unfitness

Special features of illness in the old people:-

- Multiple disease (pathology)
- Effect of pre-existing disease processes
- Altered presentation of illness e.g. electrolyte disturbance, constipation and confusion
- Adverse reactions to drugs
- Prolonged recovery time
- Adverse social problems

Special features …

- **IMMOBILITY - simple illness can immobilize the elderly = clinical problem**
- **MENTAL CONFUSION**
  - **likely in already forgetful person**
  - **by any of the commonly used drugs**
  - **severe infection e.g. pneumonia, septicaemia**
  - **metabolic problems e.g. renal, hepatic problems**

- **FALLS & HYPOTENSION - due to many things e.g. diuretics, psychotropics**
- **INCONTINENCE - due to many things including drugs**
- **CONSTIPATION – anticholinergics and many tranquillisers, bad bowel habits** etc

PHYSIOLOGICAL CHANGES

- CO reduced – BF to kidney and GIT reduced
- ↑ed tendency towards achlorhydria and reduction in the volume of gastric secretions
- Active transport of endogenous sugars, vits, and minerals across the intestines may be diminished.

- **Increased GI transit time, constipation and impaired bowel function → laxative abuse**
- **Changes in body composition with increasing age (25→ 70 years):- Fat 14 → 30%; water 61 → 53%; cell solids 25 →17%**
- **↓ in albumin concn and ↑ in alpha$_1$- acid glycoprotein**

Physiological changes cont..

- Beyond 50 years the liver mass declines as a % age of BWt accompanied by decline in hepatic BF
- Age related changes in renal function i.e. Declines in GFR, renal plasma flow, tubular secretory capacity, urine concentration ability and renal sodium conservation

PHARMACOKINETICS IN GERIATRICS

ABSORPTION

- Elevated gastric pH may affect drug ionization, dissolution, degradation and gastric emptying time
- Reduction in splanchnic BF might impair or delay drug absorption

- No major alteration in drug absorption but nutritional habits and slow gastric emptying may affect absorption of many drugs
- May be significant ↑ in F for drugs undergoing significant first pass metabolism due to ↓ed efficiency of the process

DISTRIBUTION

- Significant reduction in lean body mass → LD of digoxin might need to be decreased
- For water soluble drugs there may be significant ↓ed Vd_{ap} and ↑ed Vd for lipid soluble drugs
- ↓ed plasma protein binding of acidic drugs while binding of basic drugs may ↑

Effects of Aging on Volume of Distribution (Vd)

Aging Effect	Vd Effect	Examples
↓ body water	↓ Vd for hydrophilic drugs	ethanol, lithium
↓ lean body mass	↓ Vd for for drugs that bind to muscle	digoxin
↑ fat stores	↑ Vd for lipophilic drugs	diazepam, trazodone
↓ plasma protein (albumin)	↑ % of unbound or free drug (active)	diazepam, valproic acid, phenytoin, warfarin
↑ plasma protein (α_1-acid glycoprotein)	↓ % of unbound or free drug (active)	quinidine, propranolol, erythromycin, amitriptyline

METABOLISM

- Metabolic CL of drugs by the liver may be reduced due to ↓ liver size and mass as well as hepatic BF
- E.g: morphine, meperidine, metoprolol, propranolol, verapamil, amitryptyline, nortriptyline
- With few exceptions Phase1 processes are most adversely affected by age → prolongation of drug half life

- **Phase II conjugation processes, in particular glucuronidation and acetylation, do not appear to be significantly affected**
- **Drugs extensively eliminated in first pass via the liver show higher F**

Metabolic Pathways

Pathway	Effect	Examples
Phase I: oxidation, hydroxylation, dealkylation, reduction	Conversion to metabolites of lesser, equal, or greater	diazepam, quinidine, piroxicam, theophylline
Phase II: glucuronidation, conjugation, or acetylation	Conversion to inactive metabolites	lorazepam, oxazepam, temazepam

NOTE: Medications undergoing Phase II hepatic metabolism are generally preferred in the elderly due to inactive metabolites (no accumulation)

Other Factors Affecting Drug Metabolism

- Gender
- Comorbid conditions
- Personal habits e.g. Smoking
- Diet
- Drug interactions
- Race
- Frailty

EFFECT OF AGING ON KIDNEY

- Decreases in kidney size, renal blood flow, number of functional nephrons and tubular secretion

  Result: ↓ glomerular filtration rate (GFR)

- Decreased drug clearance of: atenolol, gabapentin, H_2 blockers, digoxin, allopurinol, quinolones

- RF declines with age even in healthy individuals in the absence of renal disease
- Both serum creat and CL_{creat} may be used as indicators of impaired RF in the elderly
- Serum creat alone not accurate in the elderly:
  - ↓ lean body mass → lower creatinine production
  - ↓ glomerular filtration rate
- Serum creatinine stays in normal range, masking change in creatinine clearance

- **The Cockcroft-Gault eqn is widely used for dose adjustments of renally excreted drugs in older people → applied in dosing of such drugs as gentamicin, digoxin & lithium**

- **Estimate (Cockcroft Gault equation) CL_{creat} =**

$$\frac{(\text{IBW in kg}) \times (140 - \text{age})}{72 \times (S_{creat} \text{ in mg/dL})} \times (0.85 \text{ for females})$$

Example: Creatinine Clearance vs. Age in a 5'5", 55 kg Woman

Age	Scr	CrCl
30	1.1	65
50	1.1	53
70	1.1	41
90	1.1	30

Limitations in Estimating CL_{creat}

- Not all persons experience significant age-related decline in renal function
- Some patients' muscle mass is reduced beyond that of normal aging
  - Suggest using 1 mg/dL if serum creatinine is less than normal (<0.7 mg/dL)
  - Not precise, may underestimate actual CrCl

PHARMACODYNAMICS

- **Response to drugs may alter with age to produce either a greater/lesser effect than is anticipated in younger adults.**
- **Age-related changes:**
  - **↑ sensitivity to sedation and psychomotor impairment with BDZs**
  - **↑ level and duration of pain relief with narcotic analgesics**

- ↑ drowsiness and lateral sway with **alcohol**
- ↓ HR response to **beta-blockers** due to ↓ in receptors
- ↑ sensitivity to **anti-cholinergic agents**
- ↑ cardiac sensitivity to **digoxin**

P’dynamics cont…

- **Baroreceptor sensitivity is decreased leading to the potential of orthostatic hypotension with drugs that reduce BP.**
- **>80yr olds are particularly intolerant to neuroleptics (confusion) & diuretics (ankle swelling that is postural)**

Non-adherence

- Rate may be as high as 50% in the elderly
- Factors in non-adherence:
  - Financial, cognitive, or functional status
  - Beliefs and understanding about disease and medications

Adverse drug events

- Responsible for 5-28% of acute geriatric hospital admissions
- Greater than 95% of ADEs in the elderly are predictable and approx 50% are preventable
- Common medications associated with ADEs:
  - Opioid analgesics; NSAIDs; Anticholinergics
  - Benzodiazepines
  - Also: cardiovascular, CNS and musculoskeletal agents

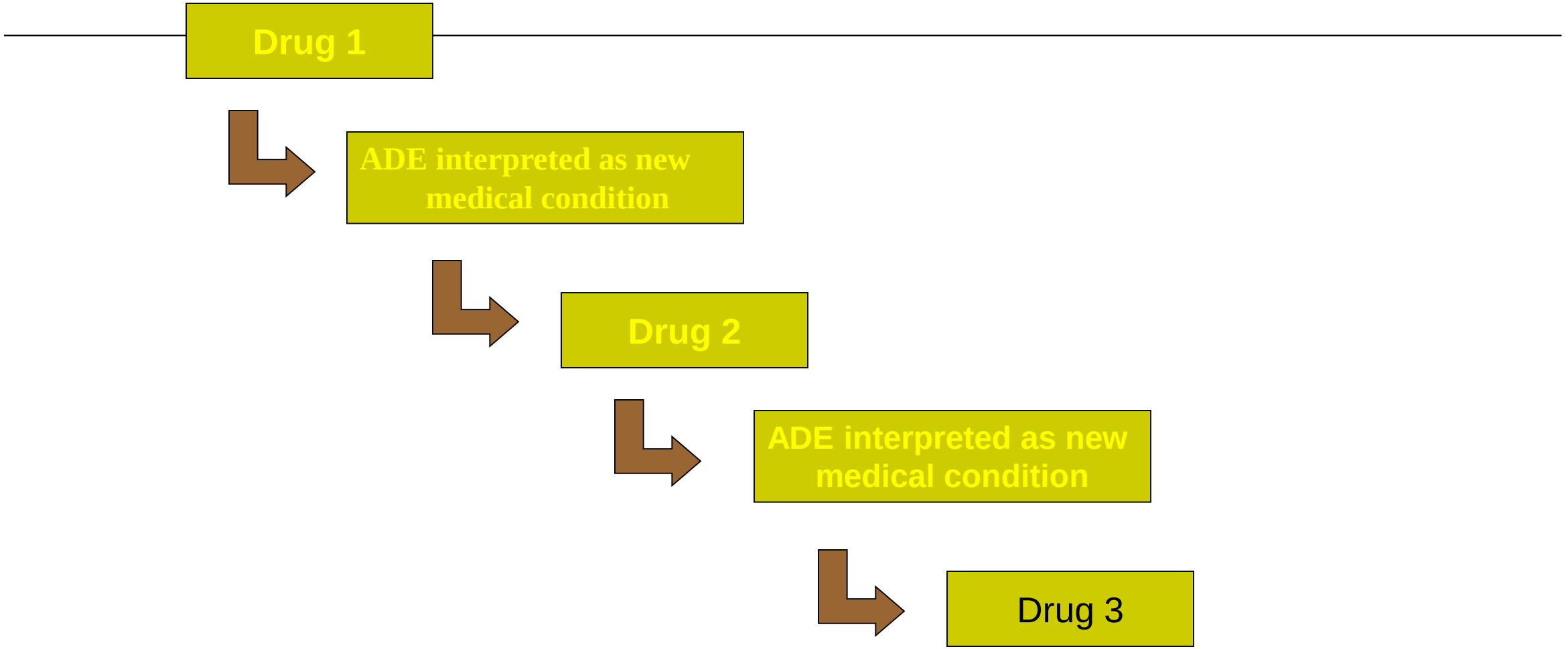
The Beers Criteria

High Potential for Severe ADE	High Potential for Less Severe ADE
amitriptyline	antihistamines
chlorpropamide	diphenhydramine
digoxin >0.125mg/d	dipyridamole
disopyramide	ergot mesyloids
GI antispasmodics	indomethacin
meperidine	muscle relaxants
methyldopa	
pentazocine	
ticlopidine	

Patient Risk Factors for ADEs

- Polypharmacy
- Multiple co-morbid conditions
- Prior adverse drug event
- Low body weight or body mass index
- Age > 85 years
- Estimated CLcreat <50 mL/min

Prescribing Cascade



Rochon PA, Gurwitz JH. Optimizing drug treatment in elderly people: the prescribing cascase. BMJ 1997;315:1097.

Common Drug-Drug Interactions

Combination	Risk
ACE inhibitor + potassium	Hyperkalemia
ACE inhibitor + K sparing diuretic	Hyperkalemia, hypotension
Digoxin + antiarrhythmic	Bradycardia, arrhythmia
Digoxin + diuretic Antiarrhythmic + diuretic	Electrolyte imbalance; arrhythmia
Diuretic + diuretic	Electrolyte imbalance; dehydration
Benzodiazepine + antidepressant Benzodiazepine + antipsychotic	Sedation; confusion; falls
CCB/nitrate/vasodilator/diuretic	Hypotension

Doucet J, Chassagne P, Trivalle C, et al. Drug-drug interactions related to hospital admissions in older adults: a prospective study of 1000 patients. J Am Geriatr Soc 1996;44(9):944-948.

Common Drug-Disease Interactions

Combination	Risk
NSAIDs + CHF Thiazolidinediones + CHF	Fluid retention; CHF exacerbation
BPH + anticholinergics	Urinary retention
CCB + constipation Narcotics + constipation Anticholinergics + constipation	Exacerbation of constipation
Metformin + CHF	Hypoxia; increased risk of lactic acidosis
NSAIDs + gastropathy	Increased ulcer and bleeding risk
NSAIDs + HTN	Fluid retention; decreased effectiveness of diuretics

GUIDELINES TO DRUG THERAPY IN OLD AGE

- There is no drug to combat senescence.
- Mere prolongation of life is not a valid aim.
- The effects of Rx must be clearly better than no Rx.
- On the other hand do not deny Rx.
- Many diseases that the elderly suffer do not respond to Rx, e.g. senile dementia.
- Consider non-pharmacologic agents.

- **Avoid prescribing prior to diagnosis**
- **Avoid starting 2 agents at the same time**
- **Minimize number of drugs →avoid polypharmacy (found in 20-40% of the old)**
- **Start with a low dose of one drug and titrate upwards on the basis of response (CNS doses should be 50% lower than for young adults)**

- Reach therapeutic dose before switching or adding a second drug
- Avoid prescribing to treat side effect of another drug
- Use 1 medication to treat 2 conditions if possible
- Use least expensive alternative

- Consider drug-drug and drug-disease interactions
- Use simplest regimen possible
- Adjust doses for renal and hepatic impairment

- Avoid some drugs e.g. chlopropamide - long half life with the risk of hypoglycaemia; anticholinergics - urinary retention
- Consider dosage form - syrup, effervescent tablets better compared to capsule etc
- Educate patient on medication purpose, benefits, safety, and potential ADEs

- **Have good knowledge of the pharmacology of the drugs that you prescribe.**
- **Maintain accurate medication records (include vitamins, OTCs, and herbals)**
- **Review medications regularly and discontinue unnecessary drugs.**

- **Monitor patients esp. the critically ill for both therapeutic and adverse effects.**
- **Where a choice exists, select a drug whose metabolism is not affected by age e.g. BDZ- Lorazepam, oxazepam instead of diazepam in mx of insomnia.**

- Drugs should be clearly labelled in large print and packed in readily opened containers → avoid child proof containers
- Utilize pill organizers or drug calendars
- Supervision of therapy may be necessary e.g. by relative, friend, neighbour etc.

Successful pharmacotherapy means using the appropriate drug at the appropriate dose for the appropriate indication in an individual patient

COMMENTS

- Elderly people are poorly represented in clinical trials with ~ 35% of published trials excluding older people on basis of age.
- E.g. >60% of cancer occurs in people >65 yrs of age, but <30% of people in clinical trials of anti cancer agents are in this group.

- **E.g. Age is the major risk factor for heart disease, yet a review of 214 MI cases found that 60% excluded elderly patients on basis of age.**
- **ADRs in the elderly are more likely to be severe & less likely to be reported by the patient.**

- **Thus much of geriatric practice with respect to drug use is based on extrapolation from studies in young patients or healthy older people.**

12. POISONING
LEVEL VI MBCHB
2019

COMPILED BY NAILA KAMADI

Outline

Management of poisoning

Antidotal therapy

MANAGEMENT OF POISONING

BY: DR. INDALO

INTRODUCTION

- All chemicals have the potential to be poisonous taken in large enough quantities
- Poisoning occurs when exposure to a substance adversely affects function of any organ system

- Poisonings and drug overdoses can cause quick physical and mental changes in a person
- The most common routes of exposure in poisoning are inhalation, ingestion and injection
- Toxic chemical reactions compromise CV, respiratory, CNS, hepatic, GI and renal systems

Toxicity may be caused by:-

- **Drugs**
- **Insecticides/herbicides**
- **Plant or animal toxins**
- **Chemical weapons**
- **Radioactive elements**
- **Household cleaning products**
- **Toxic fumes**

Mx OF POISONING – 7 COMPONENTS

- Diagnosis
- Clinical assessment
- Removal of poison from gut or skin
- General supportive & non-specific therapeutic measures
- Hastening of drug elimination
- Measures specific to the drug – antidotes etc
- Psychiatric assessment

RESURCITATION

- First priorities are ABC’s
- Vital signs including pulse oximeter and hypoglycaemia must be corrected
- Unresponsive patients treated emperically with coma cocktail : naloxone, oxygen, 50 ml of dextrose 50% in water (D50W) and 100 mg thiamine
- Thiamine prevents Wernicke’s encephalopathy - neurological symptoms caused by biochemical lesions of the CNS after exhaution of vit B reserves, particularly vit B1)

COMPONENTS OF IMMEDIATE MANAGEMENT

- Respiratory function
- Circulatory (CV) function
- Level of consciousness
- Temperature
- Convulsions
- Cardiac arrhythmias
- Gastric lavage & ipecac induced emesis
- Fluid and electrolyte balance
- Specific emergency measures
- Chest X-ray
- Collection of specimens
- Hastening drug elimination

General Management -History

- Applies to ANY episode of Poisoning
- WHAT
- HOW MUCH (Ideally mg/Kg)
- WHEN
- WHAT ELSE (Including Alcohol)
- WHY
- Use Paramedics, friends, relatives etc

DIAGNOSIS

- May be straight forward
- History may not be straight forward→ differential diagnosis in assessment of an unconscious patient
- Even if history has been given, the incriminated drug might not be the drug taken and other drugs might have been taken instead or in addition

OTHER USEFUL PIECES OF INFORMATION

- Number of tabs/caps taken
- Was alcohol also taken?
- The time of overdose ~ helps to decide to induce emesis or gastric lavage; or interpretation of plasma [drug] measurement e.g. paracetamol
- Vomiting or haematemesis ~ possibility of aspiration in a drowsy or comatose patient
- Past history ~ might give clue to drugs readily available to the patient

RESPIRATORY FUNCTION

- Maintain a clear airway at all times
- Clear out all oropharyngeal obstruction/debris/secretions
- If no cough reflex → insert endotracheal tube and measure blood gases ~ may be necessary to remove the flaccid tongue out of the airway
- If hypoxic give O_2 in amounts depending on the blood gases

CIRCULATORY FUNCTION

- Check HR and BP → Min acceptable systolic BP is 80 mm Hg in patient aged <50 years or 90mm Hg if aged > 50 years
- If hypotensive, raise the foot of the trolley/bed about 20 cm
- If BP remains low, set up an i/v infusion and give plasma expanders such as fresh frozen plasma or colloid solutions
- Avoid causing fluid overload

Circulatory function cont…

- If volume expanders do not cause rise in BP or if fluid overload occurs a β-adrenoceptor agonist such as dobutamine by continuous i/v infusion
- If chief concern is renal blood flow give low doses of dopamine or may combine it with dobutamine

NB:-

- **Dopamine and dobutamine low doses have β-adrenoceptor agonist effect BUT higher doses have α–adrenoceptor agonist effect resulting in peripheral and renal vasoconstriction**
- **Whatever drug the systolic BP should not be raised above 100 mm Hg**
- **Monitor urine output carefully, if necessary by catheterization**

LEVEL OF CONCIOUSNESS

- Will have been roughly assessed while assessing respiratory and cardiovascular functions
- Useful STD stimuli → rub sternum vigorously with knuckles or by pinching the Achilles' tendon

TEMPERATURE

- Take temperature. Rectally with low grade clinical thermometer or thermocouple if patient unconscious.
- Hypothermia (rectal temp below 36^0 C) → treat slowly by keeping patient in a warm environment or by use of a foil (space) blanket
- Severe cases (rectal temp. below 30^0 C) → more rapid warming necessary. In adults put one arm into water at 40^0 C and in the young immerse whole body in water at 40^0 C
- Warm all inspired air and infusion solutions
- Hyperthermia Tx → fanning and tepid sponging. In severe cases give chlorpromazine 100 mg i/m

CONVULSIONS Tx

- **Diazepam (10 mg i/v, repeat at 30 min intervals to a total of 30 mg and followed if required by i/v infusion at rate of 100 micrograms/kg/hr in N/Sal) OR chlormethiazole (40 – 100 ml of 0.8% solution given by i/v infusion over 5 - 10 mins, followed if necessary by a continuous i/v infusion at a rate depending on the patient's response)**
- **If no response anaesthetize the patient and treat with NM blocking drugs and assisted ventilation**

CARDIAC ARRHYTHMIAS

- Record full ECG and monitor cardiac rhythm in patients who are deeply unconscious or hypothermic or have taken digoxin, anti-arrhythmic drugs, beta adrenoceptor agonists, anti-cholinergic drugs (e.g. tricyclic antidepressants), potassium or sympathomimetic drugs
- If arrhythmias occur check for and correct electrolyte abnormalities (especially hypokalaemia), hypoxia and acidosis

CARDIAC ARRHYTH cont..

- If continuous ventricular tachycardia & ventricular fibrillation treat by direct current shock
- If other ventricular arrhythmias need to be treated then conventional drug Tx should be used
- For digitalis-induced arrhythmias → phenytoin is the drug of choice
- Supraventricular arrhythmias generally do not need Tx
- If sinus bradycardia → atropine may be used , but transvenous pacemaker may be required

GASTRIC LAVAGE AND IPECAC-INDUCED EMESIS

- If patient seen within 4 hrs of all drugs
- Within 8 hrs of taking drugs with anti-cholinergic effects e.g. tricyclic antidepressants
- Up to or more than 24 hrs of ingesting iron salts, salicylates which may cause pylorospasm

INDUCED EMESIS

- Carried out in patients with normal cough reflex
- In an emergency induce vomiting by pharyngeal stimulation with a finger or back of a spoon
- In hospital use syrup ipecac 15 ml (10 ml in a child below 18 months) with 200 ml of water or fruit juice
- Repeat dose if no effect within 15 - 30 secs
- If no vomiting within 30-60 mins proceed with gastric lavage

**GASTRIC LAVAGE

- Check if cough reflex intact. If not insert a cuffed endotracheal tube to avoid aspiration and suction apparatus should be available
- Lay patient upon the left side , head below the level of the rest of the body. Pass a wide-bore tube via the mouth into the stomach [use 150 cm tube with a 7 mm internal diameter and extra perforations in the final 10 cm or so]
- Usual lavage fluid is warm water, but in young children N/Sal should be used
- In some cases special antidotes may be added to the lavage fluid

**GASTRIC LAVAGE cont..

- Pass lavage fluid in vols of 300ml via a large funnel held above the patient, down the tube into the stomach
- Lower the funnel below the patient to allow gastric contents to drain into a bucket or aspirate with a large syringe
- Repeat procedure until the fluid returning from the stomach is clear
- Some of the initial return should be kept for chemical analysis if later required

NB

- Don’t induce emesis or gastric lavage in patients who have taken corrosive acids (give antacids) OR alkalis (give dilute acetic or citric acid) OR any volatile substances (e.g. petroleum products such as paraffin {use activated charcoal})
- Ipecac induced emesis procedure of choice in children
- Gastric lavage preferred in adults

**NB cont…

- Ipecac induced emesis easier to carry out BUT carries risk of emetine toxicity; in minority patients it does not cause complete emptying of stomach contents; risk of aspiration if patient becomes drowsy after taking ipecac
- Added adv of gastric lavage → antidotes may be instilled directly into the stomach
- Activated charcoal may adsorb varies drugs reducing their absorption
- Activated charcoal adsorbs ipecac and renders it ineffective

FLUID AND ELECTROLYTE BALANCE

- If patient fluid depleted (e.g. because of vomiting) but conscious, oral fluids are usually sufficient
- In most unconscious patients replacement with two 500ml units of 5% dextrose for every 500ml unit of physiological saline is usually sufficient
- Central venous pressure (CVP) may be required in severely ill patients
- Hypokalaemia may be treated with either oral or i/v KCl

SPECIFIC EMMERGENCY MEASURES

- Cyanide → dicobalt edetate
- Opiates → naloxone
- Paracetomol → acetylcysteine
- Carbon monoxide → oxygen
- Paraquat → Fuller's earth
- Salicylates →
- Tricyclic antidepressants →
- Barbiturates →
- Organophosphate insectisides →
- Digitalis →

CHEST X - RAY

- Should be taken in any drowsy or comatose patient who has vomited to rule out aspiration pneumonia
- Any patient who requires endotracheal intubation, to check the position of the endotracheal tube
- Not usually necessary in fully conscious patients even after induced emesis or gastric lavage

COLLECTION OF SPECIMENS

- Gastric aspirate (drugs), urine (drugs) and admission blood [drugs, arterial gases, electrolytes] sample (20ml in two Li-heparin tubes) should be kept in case later analysis is required in:-
  - Suspected criminal poisoning
  - Any unusual poison (especially new drugs)

- Label containers carefully with full name of the patient, date and time

NB

- **Emergency analysis of drugs in blood indicated only if result will affect Mx of the patient, and is usually restricted to ASA and paracetamol**
- **Measurement of [barb] serves principally in making diagnosis in cases of coma of unknown cause and in identifying type of barb involved.**
- **Paraquat may be identified in gastric aspirate and urine → test useful in excluding diagnosis and monitoring progress**

NB cont..

- In all ill patients routine plasma urea & electrolytes measurements are performed to assess RF, Hepatic Function and state of dehydration
- In some cases carry out tests specific to the effects of the drug e.g blood glucose, arterial blood gases, prothrombin time (aspirin), liver function tests (paracetamol)

**INDICATIONS FOR LAB TESTS IN SELF POISONING

TEST	INDICATION
Plasma [drug]	→ ASA, paracet, (barb, Fe, Li)
Urine [drug]	→ Paraquat
Arterial blood gases	→ Coma, unexplained hyperventilation, hypoxia (e.g due to CO)
Plasma electrolytes (especially K^+)	→ severe ASA poisoning digoxin, S/ureas, sym/mimetics
Blood glucose	→ unexplained coma, alcohol, ASA, hypoglycaemic drugs
Prothrombin time	→ ASA, paracet (not urgent)
LFTs	→ → paracetamol (not urgent)

HASTENING OF DRUG ELIMINATION (HDE)

- Diuresis in alkaline or acidic urine for → drugs which are subject to extensive passive reabsorption by the renal tubules, and whose rate of CL_R is proportional to the rate of urine flow e.g
  - Salicylate and lithium CL_R is increased by alkaline diuresis
  - Amphetamine, quinine, quinidine, tranylcypromine CL_R increased by acid diuresis

HDE - DIALYSIS

- Hemodialysis and peritoneal dialysis reserved for severe cases of poisoning
- Useful only for drugs not widely distributed to body tissues and which are not highly bound to plasma proteins
- May be of value in serious poisoning with salicylates, barbs, chloral hydrate and its derivatives

HDE – CHARCOAL HEMOPERFUSION

- Charcoal adsorbs many drugs and can be used to remove drugs from circulation
- Of value when there is high protein binding
- May be of value in serious poisoning with salicylates, barbs, glutethimide, meprobamate, methaqualone, theophyline and derivatives of chloral hydrate

NB - Activated charcoal:-

- Most effective decontaminant for majority of poisonings except alcohol, strong acids or alkalis, KCl, or metals (Au, Li, Fe) ~ does not bind these toxins
- As effective as, or superior to, induced emesis or gastric lavage with or without activated charcoal
- Well tolerated - should be given orally (less unpleasant than nasogastric or orogastric administration) if patient is conscious.

HDE - CATHARTICS

- Decrease absorption by speeding passage thr' GIT i.e. limits contact with mucosal surfaces.
- Osmotic cathartics usually given with activated charcoal ~ decrease transit time of activated charcoal

HDE- WHOLE-BOWEL IRRIGATION

- Osmotically balanced Polyethylene glycol electrolyte solution (PEG-ES) e.g. GoLYTELY and Colyte ~ powders for reconstitution – given by NG tube or oral drink
- Induction of liquid stool by osmotically balanced electrolyte solution (1 litre)
- Indicated for cpds not adsorbed onto activated charcoal e.g. metals and for Controlled Release products, sachets/packets of drugs
- Flushes the bowel mechanically without creating electrolyte disturbances
- CI in bowel obstruction or perforation

- **PSYCHIATRIC ASSESSMENT!**

ANTIDOTAL THERAPY

BY: DR. MUASYA

13. ALTERNATIVE MEDICINE
LEVEL VI MBCHB
2019

BY: DR. OCHANDA

ECHINACEA(echinacea purpurea)

- 3 species used- Echinacea purpurea, E. pallida, E. angustifolia
- Constituents – flavonoids, lipohylic constituents like alkamides, polyacetylenes, water soluble polysaccarides and water soluble caffeoyl conjugates eg echinocoside, chicoric acid, ceffeic acid.
- Chicoric acid, alkamide and polysaccarides have immune modulating activity

Pharmacologic effects

- 1. Immune modulation- increased phagocytosis, increased production of interleukin-1, 6, 10 and TNF-αby phagocytes.
- Enhanced NK-lymphocytes activity and antibody dependent cellular toxicity.
- 2.Anti-inflammatory effects
- 3.Anti-bacterial, anti-fungal anti-viral and anti-oxidant activity

Clinical uses

- 1. In colds and other respiratory infections
- 2.To enhance hematologic recovery after chemotherapy
- 3. Adjunct treatment of UTI and vaginal fungal infections

Adverse effects

- 1.Flu-like symptoms
- 2.Unpleasant taste for oral doses
- 3.GIT upset
- 4. Headache, dizziness
- 5. Allergic reactions
- Dose 900mg/d, dried root extract, 6-9 mls of compressed juice/d in 2-5 divided doses.

FEVER FEW(tanacetum parthenium)

- Contains flavonoid glycosides, monoterpenes e.g camphor, sesquiterpene lactones(most important, parthenolide in seeds and leaves).
- Preps are standardized to contain no less than 0.2% parthenolide.

Pharmacologic effects

- 1. Migraine headaches prophylaxis. Inhibits serrotonin release and platelet aggregation.
- 2. Anti-inflammatory effects- in Rh. arthritis. PGs, thromboxane and leukotriene B4 synthesis inhibited, TNF-α and IL-1 expressed.
- 3.Other effects- inhibition of histamine release, inhibition of SM contractions, cytotoxic effect on tumor cell lines, anti-microbiol effects on gram +ve bacteria, yeasts and filamentous fungi.

Adverse effects

- 1. Mouth nulcers
- 2. GIT upset
- 3. contact dermatitis
- 4. Rebound syndrome if abruptly stopped.
- Caution with anticoagulants and antiplatelets.
- Dose 2-3 fresh leaves daily or 125mg/d dried leaves formulation.

GARLIC(Allium sativum)

- Activity is due to a variety of organosulfur compounds , most important, allicin, which is responsible for the characteristic odor.

Pharmacologic effects

1. CVS effects-

Inhibits HMG CoA reductase, anti-platetelet, mixed fibrinoloytic effects, anti-oxidant effects. Useful in atheromas.

Increases blood vessel elasticity and reduces blood pressure

2. Endocrine effects – Hypoglycemic effects

3. Anti-microbiol effects- gram +ve and gram -ve

- Candidiasis, E. histolytica and some viruses. Inhibits thiol-containing enzymes
- 4. Anti-neoplastic effects- epidemiologic evidence of prevention of esophageal, stomach and colonic Ca; breast and lung Ca.

Adverse effects

- 1.Nausea
- 2. Hypotension
- 3. Allergy
- 4. Bleeding- rare
- 5. Contact dermatitis
- 6. Breathe odor
- Doses- Preps standardize to contain 1.3% alliin, enteric coated preferred.600-900mg/d powdered garlic, equivalent to one clove raw garlic(2-3g)/d.

GINKO(Ginkgo biloba0

- Contains flavone glycosides, terpenoids i.e ginkgolides A, B, C, J, and bilobalide

Pharmacologic effects

- 1.CVS effects –increase blood flow and reduce viscocity. Useful in intermittent claudication.
- 2.Metabolic effects- anti-oxidant and radical scavenging activity- reduces ischemic injury and reduces markers of oxidative stress.
- 3. CNS –treats cerebral insufficiency and Alzheimer's disease. Increases neurotransmitters activity, inhibits MAO A and B, inhibits steroid synthesis, reduces amyloid-β fibril formation.

- 4. Others –Anti-platelet and anti-inflammatory effects, chronic tinnitus improvement. Studies on asthma, erectyle dysfunction,hearing loss and short term memeory inconclusive.

Adverse effects

- 1.Nausea, Stomach upset, diarrhea
- 2. Allergy
- 3. Anxiety and insomnia
- 4. Bleeding when used with ASA or warfarin

- Dose- Leaf preps standardized to contain 24% flavone glycosidesa and 6% terpene lactones. Dose 120-240mg of dried leaf extract in 2-3 do

GINSENG

- From genus panax- panax ginseng(Chinese, Korean), P. quinquefolium(American).
- constituents- Dozen Triterpenoid saponin glycosides called ginsenosides and panaxosides. Preps standardized to contain 7% ginsenosides.
- Others –Siberian ginseng(Eleutherococcus senticosus),Brazilian ginseng(Pfaffiapaniculata

Pharmacologic effects

- 1.Immunomodulation
- 2. Egogenic activity
- 3.Nootropic(mind enhancing) activity,
- 4.Vasoregulatory effects
- 5.Antiflammatory effects
- 6.Anti-stress activity
- 7.Anaelgesia
- 8.Antiplatelet activity

- 9.Improved glucose homeastasis
- 10. Anticancer properties

Clinical uses

- Several studies suggestive of usefulness in 1.improving physical and mental perfomance, 2.lowering postprandial glucose and
- 3.reduction in several types of cancer.
- Non conclusive so far.

Adverse effects

- 1. Vaginal bleeding and mastalgia
- 2.Insomnia, nervousness
- 3.Hypertension in high doses(>3gm/d) of panax ginseng.
- Dose- 1-2 gm crude P.ginseng root or equivalent
- Siberian ginseng, 2-3gm/d

KAVA(piper methysticum)

- Root extract of paper plant. Used for relaxing properties like alcohol.
- Has lipophylic and hydrophylic components. Active constituents arekavalactones and kavapyrones.The activeenolides and dienolides are kawain(kavain), methysticin, yangonin.

Pharmacologic effects

- 1. CNS- same actions as benzodiazepines. Also inhibits glutamate release, inhibits NE reuptake, reversible MAO B inhibition and dopamine antagonism. Mild anticonvulsant activity.
- 2.Antiplatelet action

Clinical use

- Anxiety

Adverse effects

- 1.Tingling in mouth and GIT upset
- 2. euphoria, sedation, visual and auditory changes. Ataxia, muscle weakness, paraesthesia in high doses.
- 3. Dystonic extrapyramidal reactions
- 4. uterine contractions and apperas in milk
- 5.Ichthiosiform skin reactions, associated with facial swelling and photosensitivity

- Sebacious gland eruptions noted.
- 6. Hepatitis and Hepatic necrosis

- Doses- 50-70mg purified kavalactones three times daily. Equivalent to 100-150mg dried kava root extracts.
- For hypnotic 180-210 mg 30 min - 1hr before bed. Limit use to 3 months.

MILK THISTLE(Silybum marianum)

- Fruit and seeds contain lipophylic mixture of flavonolignans called silymarin. Silymarin comprises 2-3% dried herb, made of 3 primary isomers sylibinin, silychristine and silydianin. Silybin is the mostprevalent and potent making up 50% silymarin complex.
- Standard preps contain 70-90% silymarin.

Pharmacologic actions

- 1.Liver disease
- Prophylactic against liver injury
- Antiflammatory
- Anti-cirrhosis
- Helpful

management of hypercholeterolemia

- Thought to be Helpful in treatment of hypercholesterolemia and gallstones
- 2. Chemotherapeutic effects
- Reduces tumor initiation and promotion in skin ca, Breast and prostate Ca

Adverse effects

- Loose stools associated with increased bile secretion at high doses.

ST JOHN’S WORT(hypericum perforatum)

- Contains hypericin, hyperforin. Flower extracts in methanol used.

Pharmacologic effects

- 1.Antidepressant action
- Inhibits serrotonin, NE and dopamine reuptake. Down regulates cortical-β adrenoceptors and upregulates expression of serotonin receptors. Opioid and GABA receptors activity also shown.
- 2. Antiviral activity – HIV killing and a variety of enveloped and non-enveloped viruses on activation with UVA light.

- 3. Anti-carcinogenic effects
- Shown to be effective in basal cell and squamous cell ca treatment given intralessionally.

Adverse effects

- 1. Photosensitization. Use sunscreens.
- 2.Hypomania, mania and autonomic arousal.

- Dose –Products standardized to contain0.3% hypericin. Hyperforin should be 2-5%.
- Mild to moderate depression -900mg dried extract in3 divided doses/d. effects seen at 2-4 wks

SAW PALMETTO(seronoa ripens or sabal serrulata)

- Berries Contains phytosterols(β-sitosterol), aliphatic alcohols, polyprenic compounds and flavonoids. Marketed extracts arelipophylic extracts containing 85-95% fatty acids and sterols.

Pharmacologic action

- 5^{α}-reductase inhibitor used in treatment of BPH. It also inhibits DHT binding to androgen receptors.
- Effects seen at 3 months

Adverse effects

- 1-3%
- Hypertension
- Decreased libido
- Abdominal pain
- Impotence
- Headache
- Git upset
- Dose -160mg orally BD.x3-6months.

PURIFIED NUTRITIONAL SUPPLEMENTS

- DHEA- for wt loss, decreased choleterol levels, prevennt aging, treatment of Alzheimer's disease,, prevention of HIV/AIDS, SLE treatment, amelioration of insulin resistance in diabetes
- A/E – BPH, Ca prostate other hormonal cancers may be promoted, endocrine effects
- Dose 25-50mg/d in women, 25-100mg in men

- MELATONIN
- Used for treatment of jet lag,insomnia, prevention of ovulation. Causes reduced sperm quality.
- A/E –next day drowsiness, tachycardia, depression, vivid dreams,, headache
- Dose 5-8mg evennings for jet lag, 0.3-10mg nocte for insomnia

Someone's sitting in the shade today because someone planted a tree a long time ago.

#service

- Warren Buffet -

#Glory_To_Jesus_Christ