



PHARMACOLOGY SUMMARY

FINAL - HLS

2023-2024

made by : ebaa alzubi



ANTICOAGULANT

most common Adverse Effect : bleeding

Indirect thrombin inhibitor

Unfractionated Heparin (UFH)

Mechanism of Action: binds to antithrombin ,inhibits factor IIa, IXa, Xa, and XIIa

administeration route :continuous intravenous infusion

•Intramuscular = risk of bleeding & hematomas

antidote : Protamine sulfate in 5 min

Adverse Effects : bleeding , bone loss and osteoporosis , HIT

Drug–drug Interactions: aspirin, NSAIDs, dipyridamole, or sulfinpyrazone (any drug enhances bleeding)



HIT :
antibodies activate platelets = **arterial** thromboembolic .
never ever take any type of heparin again

Sulfinpyrazone is used to treat gout///APTT : test for heparin bleeding time

Low-Molecular-Weight Heparins (LMWH)

Enoxaparin, Dalteparin

Mechanism of Action:activates antithrombin against factor Xa ,limited against thrombin levels are not generally measured except in renal insufficiency, obesity, and pregnancy

Advantages :predictable , dose-independent , longer half-life , Less monitoring , weight based

Adverse Effects : bleeding , osteopenia and osteoporosis , HIT (less than UFH)

Drug–drug Interactions: aspirin, NSAIDs, dipyridamole, or sulfinpyrazone (any drug enhances bleeding)

administeration route : SC administration

Fondaparinux

Mechanism of Action: pentasaccharide units that bind reversibly to antithrombin
inhibits only factor Xa activity 10

administeration route : SC administration

once-daily dosing .prevention of **venous** thromboembolism

persists for 2 - 4 days following discontinuation

No antidote

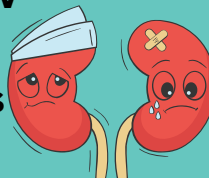
Adverse Effects : bleeding , rare HIT

Direct factor inhibitors

Hirudin is derived from Leech

Lepirudin

Irreversible ,inactivates fibrin-bound thrombin , IV or SC , aPTT , renal excretion , for thrombosis related to HIT



Bivalirudin

inhibits both circulating and clot-bound thrombin, **reversibly** , IV , less bleeding risk , for percutaneous coronary intervention (PCI) and HIT .
NOT affected by antiphospholipid antibodies .
contraindicated in severe renal impairment



Warfarin

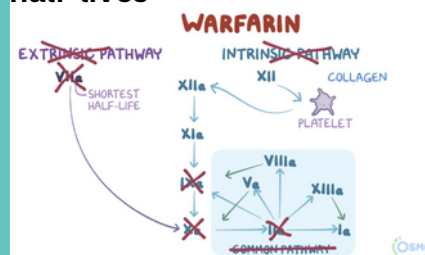
inhibits the reduction of vitamin K epoxide, reducing the formation of s II, VII, IX, and X, dependent on coagulation protein elimination half-lives

continuous patient monitoring

given orally

Vitamin K is the antidote

Adverse Effects: Bleeding, "Purple toe syndrome", skin necrosis in the first week of therapy



increase INR

increase bleeding chance if taken with :azole, NSAIDs, statins, cimetidine, omeprazole

decrease INR

inducer of enzyme - against warfarin : smoking, rifampin, contraceptive, cholestyramine.

Warfarin resistance can be due to mutations in CYP2C9 and the gene coding for VKOR receptor gene

Direct Oral Anticoagulants

Drug-drug Interactions: aspirin, NSAIDs, dipyridamole, or sulfinpyrazone (any drug enhances bleeding)

Adverse Effects: Gastrointestinal complaints, Bleeding, arterial fibrillation

Rivaroxaban, apixaban, and edoxaban

inhibitors factor Xa
CYP3A4, and P-glycoprotein.

10

hip or knee replacement surgery

extended venous thromboembolism (VTE)

Dabigatran

direct factor IIa inhibitor

2

extended venous thromboembolism (VTE)

Thrombolytic Agents

Given by intravenous

dissolves intravascular clots by the action of plasmin, a protease

Therapeutic uses: Acute myocardial infarction, Central DVT, Sever PE, Acute ischemic stroke

6

3

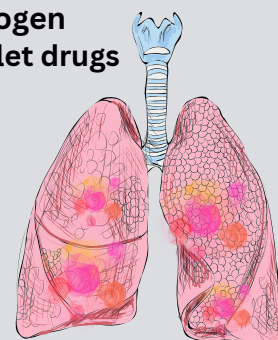
Streptokinase

by Lancefield group C β-hemolytic streptococci
requires a loading dose
converts plasminogen to plasmin

Adverse Effects: Bleeding - systemic
lytic state, Allergy, Anaphylaxis,

Tissue Plasminogen Activator (tPA)

high affinity and activates plasminogen
Re-occlusion by heparin and antiplatelet drugs



antidote :

Aminocaproic acid, Tranexamic acid
prevent plasmin from work

Contraindicated in (DIC), and bleeding from kidney or ureters

D

- First Generation TAs:
 - .1Streptokinase
 - .2Urokinase
- Second & Third Generation TAs:
 - .1tPAs: Alteplase, Reteplase, Tenecteplase

Antiplatelet Drugs

Platelets participate in atherosclerosis management of Myocardial infarction

Aspirin

Irreversible inhibitor

lasts for the life time of the platelet (7-10 days)
low doses : blocking the production of thromboxane A₂

Eicosapentaenoic Acid

- Unsaturated fatty acid present in cold water fish.
- Generates PGI₃ and TXA₃
- PGI₃ is an effective anti-aggregating agent like PGI₂, while TXA₃ is much less active than TXA₂

Clopidogrel

irreversibly block the ADP P2Y₁₂ receptor
Patients who require aspirin but can not take it
coronary stents

Severe Neutropenia

Thrombotic thrombocytopenic purpura

Cholestatic hepatitis



GPIIb/IIIa Receptor Blockers

final common pathway for platelet aggregation.
acute coronary syndromes parenterally

Abciximab : antibody

Cancer Chemotherapy

Alkylating agents

affect all cell life stages , bind to guanine n7 on DNA , causing cross linking - cell death .

Nitrogen Mustards

Cyclophosphamide

prodrug - orally - converted by liver cytochrome P450

side effects : cardiotoxicity, hemorrhagic cystitis, "bladder burn", or hematuria

toxicity correction : mesna

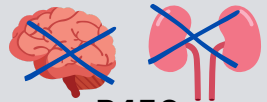


Ifosfamide

prodrug - IV - greater activity - converted by liver cytochrome P450

side effects : neurotoxicity , nephrotoxicity , hemorrhagic cystitis, "bladder burn", or hematuria

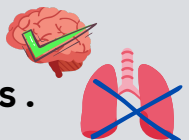
toxicity correction : mesna



Nitrosoureas

inhibits DNA, RNA , lipid soluble , side effect : pulmonary fibrosis .

Carmustine (BCNU) : IV - Lomustine (CCNU) : -orally



Alkyl sulfonates Busulfan

orally - cause pulmonary fibrosis



Nonclassic Alkylating Agents

Procarbazine (PO) and Dacarbazine (Parenteral) - more carcinogenic - acute leukemia , Potent vesicants , CNS toxicity: neuropathy, ataxia, lethargy

Antimetabolites

Methotrexate (MTX)

a folic acid analog, inhibits dihydrofolate reductase, DNA, RNA, **purine** and proteins
polyglutamates are selectively retained within cancer cells
Resistance develops: ↓ folate carrier ↓ polyglutamate ↑ target enzyme - altered affinity
↑ transporter P170 glycoprotein
aspirin decrease its renal excretion. **orally - 26** adverse effect: Mucositis
leucovorin (5-formyltetrahydrofolate) rescue normal cells.

Cytarabine (Ara-C)

S phase specific antimetabolite, inhibits DNA polymerase- α & β , IV, Mucositis, Neurotoxicity

Platinum complexes

crosslinks with GG base IV administration DOSE LIMITING toxicity: **neuropathy**,
hearing loss "ototoxicity"

Cisplatin

more toxic
more chemically reactive
neurotoxicity.

Carboplatin

longer half-life
less effective

Vinca alkaloids

inhibits tubulin polymerization, metaphase arrest,

Vinblastine vesicant

periwinkle, mucositis, Syndrome of inappropriate ADH secretion (SIADH) and alopecia.

Vincristine

periwinkle, neuropathy, Syndrome of inappropriate ADH secretion (SIADH) and Ataxia.
seizures and coma.

Epipodophyllotoxins

Mayapple root, double oral, topoisomerase II and DNA,

Antitumor Antibiotics

strains of soil Streptomyces, DNA intercalation

Doxorubicin, Daunorubicin

Mechanism: Generation free radicals, Inhibition of topoisomerase II.
administered IV, cardiac toxicity: arrhythmias, ECG changes.
antidote: Dexrazoxane

Bleomycin

contains a DNA-binding region, and an iron binding domain
free radical formation, G2 phase
Adverse effects: Pulmonary toxicity, allergic reaction

IV

Tyrosine Kinase Inhibitors

Imatinib

inhibitor of the tyrosine kinase , no ATP , treat t(9:22) Philadelphia chromosome translocation .
orally Fluid retention , Myalgias

Asparaginase

L-asparagine amidohydrolase , less ammonia , Hypersensitivity reactions , Pancreatitis,

Proteasome Inhibitors -Bortezomib

dipeptide boronic acid analogue , Complete AV-block , plasmacytomas

Monoclonal Antibodies

MONOCLONAL ANTIBODIES: "-MAB"

adverse effect : melena , Swelling , Chest tightness

Alemtuzumab

humanized IgG1 with a kappa chain , treatment of B-cell chronic lymphocytic leukemia ,
causing lysis - pancytopenia

Rituximab

chimeric murine-human monoclonal IgG1 , for relapsed or refractory low-grade or follicular B-cell
non-Hodgkin's lymphoma

Antimalarial Drugs

Plasmodium falciparum = most severe

Plasmodium vivax & Plasmodium ovale = dormant hypnozoite

Plasmodium malariae(erythrocytic)

A fifth species, P knowlesi = monkeys

infection : enter as sporozoites , in liver
as (schizonts) , in RBCs merozoites , exit
as gametozoite

Chloroquine

highly effective blood schizonticide -moderately effective against gametocytes

not effective only for P.vivax and P.ovale not for P falciparum= resistant

Mechanism of action :inhibits heme polymerase , heme is toxic for parasite

Mutation in (PfCRT)&MDR 1 develop resistance

orally - long half-life - Kaolin, and Calcium and magnesium interfere -

8-aminoquinolone
after chloroquine

uses :Acute attacks of non-falciparum and falciparum-sensitive malaria ,
Chemoprophylaxis , Amebic liver abscess .

Adverse effects:

QRS and T wave abnormalities , retinopathy , Pruritus , Ototoxicity , G6PD hemolysis
, Exfoliative dermatitis , cardiac arrest , neuropathy and myopathy

Quinine(1820) and Quinidine

from Cinchona tree ,affect the feeding mechanism , Resistance is uncommon , given
with Doxycycline or Clindamycin .

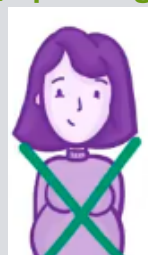
Adverse effects:

Cinchonism: Tinnitus, visual disturbances. Later, auditory abnormalities , //Blackwater fever
- Blood dyscrasias , Hypersensitivity , uterine contractions. Hypotension, QT prolongation.

Primaquine

treat: P vivax and P ovale , +chemoprophylaxis , Active against hypnozoites

Adverse Effects: Hemolysis in G6PD , Methemoglobinemia , Leukopenia,
agranulocytosis ,Cardiac arrhythmias



Antivirals

drugs block : virus attachment , penetration , uncoating , early& late protein synthesis , packaging.

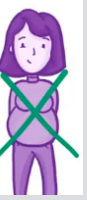
Acute infection = Influenza, Rubella , **Latent** infection: Chickenpox, Herpes simplex, **CMV**, **Chronic** infection : **HIV**, Hepatitis C

Agents for Cytomegalovirus (CMV)

advanced immunosuppression, reactivation of latent infection.
cause : retinitis, colitis, esophagitis, CNS disease, and pneumonitis

Ganciclovir

acyclic guanosine analog that requires activation by triphosphorylation (virus enzyme) , selectively activated inhibits the viral DNA polymerase IV, PO, or via intraocular implant excreted by kidney resistance
Adverse Effects: Hepatotoxicity , CNS toxicity , **carcinogenic**, **embryotoxic** and may cause **aspermato-genesis**



Maribavir (Livtency)

new ,first-in-class , treat post-transplant , Inhibitor of cytomegalovirus pUL97 kinase =
X replication
ganciclovir antagonist , Side effects: Change of taste , GI pain

Agents for Human Immunodeficiency Virus

Combination therapy , immature non-infectious Varion into infective by proteolytic cleavage .

Nucleoside and Nucleotide Reverse Transcriptase Inhibitors

competitive inhibition of HIV-1 reverse **transcriptase** , premature chain termination , mitochondrial toxicity due **gamma** inhibition , fatal lactic **acidosis** with hepatic steatosis , risk of myocardial infarction

Abacavir

guanosine analog ,Hypersensitivity , **Test HLA-B*5701** , Elevation of aminotransferases and creatine kinase levels **↑MI**

Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)

bind directly ,Do not require phosphorylation , GIT intolerance and skin rash (Steven-Johnson syndrome)
Metabolized by CYP3A4, so any anti malarial inhibits cytochrome p450 , should be avoided .

Delavirdine

Pregnancy should be avoided.
• Extensively metabolized by CYP3A and CYP2D6 and also inhibits CYP3A4 and CYP2C9



Protease Inhibitors

inhibit this post-translational cleavage = production of immature, noninfectious viral particles.
active against HIV-1 and HIV-2 , do not need intracellular activation
cause : **central obesity** ,**buffalo hump** , Cushingoid appearance , metabolized by CYP3A4
fat + insulin resistance except **atazanavir**

Atazanavir

hyperbilirubinemia and jaundice due to inhibition of UGT1A1
Prolongation of PR interval and QTc **↑**

Fusion Inhibitors

binding of the viral envelope glycoprotein complex (gp120 & gp41)

Enfuvirtide

blocks entry ,binds to gp41 , sc injection , proteolytic hydrolysis
,eosinophilia **↑** bacterial pneumoni

Integrase Strand Transfer Inhibitors

Raltegravir

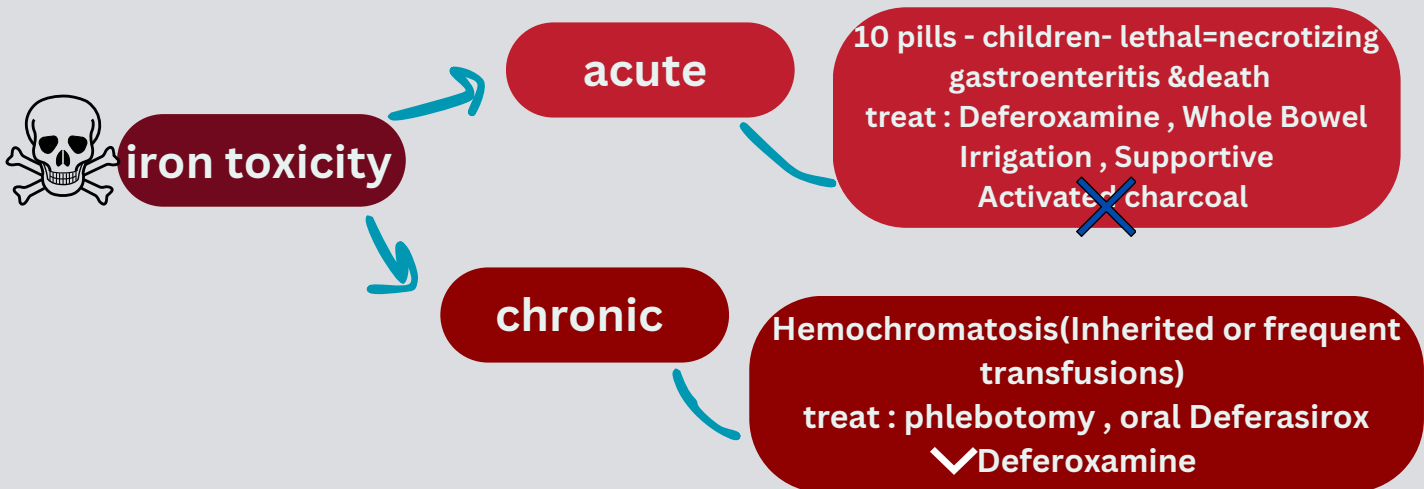
pyrimidine analog , binds integrase ,both HIV-1 and HIV-2 , inhibits strand transfer, the third and final step , (Ca2+, Mg2+, Fe2+) interfere , Increased creatine phosphokinase

Drugs Used in Anemias

Essential elements:

IRON

Iron deficiency is the most common cause of chronic anemia – microcytic hypochromic anemia
men have more iron Contant growth , pregnancy , menstruation need more iron intake
absorbed **duodenum and proximal jejunum** in vegetables and grains ,well absorbed from meat
absorbed as ferrous Fe^{+2} by the divalent metal transporter (**DMT1**) ///go to blood by ferroportin (FP)
stored as ferritin in apoferritin enters maturing erythroid cells by transferrin receptor-mediated
endocytosis , stored as ferritin in macrophages , lost by exfoliation of intestinal mucosal cells .
increase iron loss : Gi **bleeding** (peptic ulcers=black stool) , **ESKD** (hemodialysis) , **Menstruation** .
Inadequate iron absorption: **Gastrectomy** , Severe small bowel disease .
Treatment: orally daily supplement (Ferrous & Ferrous sulfate hydrated & gluconate & fumarate) **25%** .
Adverse effects: Gi discomfort, **constipation** and diarrhea , Black stools
antibiotics= tetracyclins = precipitate metals= **IRON MALABSORPTION**
for whom can't take oral (tolerate absorb , Anemia With extensive chronic blood loss)= **IV given** ✓
IV irons : dextran (hypersensitivity , irritation , bronchospasm) , **sucrose complex & sodium gluconate**



Vitamin B12

a porphyrin-like ring ,Deoxyadenosylcobalamin or Methylcobalamin , absorbed in the terminal ileum
by endocytosis (factor from stomach + vit B12) , deficiency COMMON DUE TO MALABSORPTION
.transported by **transcobalamin II** >>. present in meat
(less **HCL** , **H.pylori** , **PPI** , **metformin** = CAUSE B12 MALABSORPTION)
methylmalonyl-CoA accumulates **folate cofactors become deficient** = “methylfolate trap”
methionine synthesis cause neurological manifestations
administration of folic acid **CORRECTS** anemia **not** neurological manifestations .
treatment by IV cyanocobalamin or **hydroxocobalamin** ✓

Folic Acid

required for the synthesis of amino acids, purines and DNA ,pteroylglutamic acid(1, 3 , poly) .
deficiency cause : Megaloblastic anemia , Congenital malformations – neural tube defects, such as **spina bifida and anencephaly** , Occlusive vascular disease due to **homocysteine** accumulation.
in yeast, liver, kidney & green vegetables pregnant needs more
absorbed in the proximal jejunum stored in liver orally supplement till find the cause
Drugs: **Methotrexate**, trimethoprim, pyrimethamine inhibit **dihydrofolate** reductase
B. Long-term **phenytoin** therapy impair folate **absorption**

Hematopoietic Growth Factors

Erythropoietin

formed by the kidney ,stimulates hematopoiesis + induce reticulocyte , corrects the anemia (not iron def, anemia & bone marrow impairment) <<<<anemia of chronic renal failure= less EPO& less hematocrit . we give patient (**epoetin alpha**) ✓
- Anemic individuals usually have increase in EPO levels
EPO treats anemia of chronic renal failure //may Iron and folate supplementation
Adverse Effects: hypertension and thromboembolic complications ,(humanized EPO = no allergy)

Myeloid Growth Factors

Recombinant human G-CSF (rHuG-CSF): **Filgrastim**
stimulates neutrophil lineage & prolongs their survival .

used in case of Cancer
Chemotherapy-Induced
Neutropenia
Adverse effects : Capillary leak
syndrome , Splenic rupture

Recombinant human **GM-CSF** (rHuGM-CSF): **Sargramostim**
stimulates early and late granulocytic, erythroid and megakaryocyte progenitors.

Megakaryocyte Growth Factors

Thrombopoietin and interleukin-11 (IL-11) are endogenous regulators of **platelet production**.

ROMIPILOSTIM
* RECOMBINANT THROMBOPOIETIN

ELTROMBOPAG
* AGONIST to THROMBOPOIETIN RECEPTOR on MYELOID PROGENITOR CELLS
* STIMULATE MEGAKARYOCYTE PRODUCTION
* LIVER TOXICITY
* SEVERE BLEEDING

STIMULATE PLATELET PRODUCTION
THROMBOCYTOPENIA

TREAT DISORDERS where the body starts BREAKING DOWN PLATELETS
CHRONIC IMMUNE THROMBOCYTOPENIA

SIDE EFFECTS
* ↑ RISK of CLOT FORMATION
* ↑ in PLATELET PRODUCTION

Eltrombopag

orally active small agonist
treatment of thrombocytopenia in patients with hepatitis C & inadequate response
Adverse effects: Hepatotoxicity , **Portal vein thrombosis**

Romiplostim

agonist , treat chronic immune thrombocytopenia
Adverse effects: Portal vein thrombosis & acute myeloid leukemia risk & BM fibrosis & Rebound thrombocytopenia

Portal vein thrombosis

Oprelvekin

Recombinant form of IL-11 ,
adverse effect : Transient atrial arrhythmias & Anemia & Dyspnea & Hypokalemia

اللهم إني أسألك أنك العليم الكريم أن توفقنا لما تحبه وترضى، وأن
تكتب لنا النجاح والفلاح والتوفيق في تحصيل كل علم نافع، اللهم
مالك السماوات والأرض ومنزل الكتاب لا تنزع العلم من بيننا
وارفعنا به، وارزقنا يا الله فهم أنبيائك وحفظ الملائكة ورسلك

