Pharmacokinetic and pharmacodynamic drug interactions

Drug interactions
Lecture 1

- Introduction
- Absorption based interactions

Drug interaction

When 1 drug alters the effects of another drug

e.g. Drug A causes Drug B to have ...

- Increased or reduced effect
- Slower or more rapid effect
- New or increased side effects

TYPE OF INTERACTION

Unidirectional

Bidirectional

Pharmacokinetic & Pharmacodynamic interactions

Me

Pharmacokinetic: Amount of drug in blood is altered

Pharmacodynamic: Amount of drug in blood remains the same, but its effect is altered

ADME

Absorption

Distribution

Metabolism

Excretion

Absorption based interactions

One drug make the absorption of another drug …

- Faster or slower
- Less or more complete

Mechanisms

- pH
- Gastric emptying and intestinal motility
- Physico-chemical interaction

Changes in pH of G.I.T. contents

Stomach pH is variable.

Antacids pH ↑

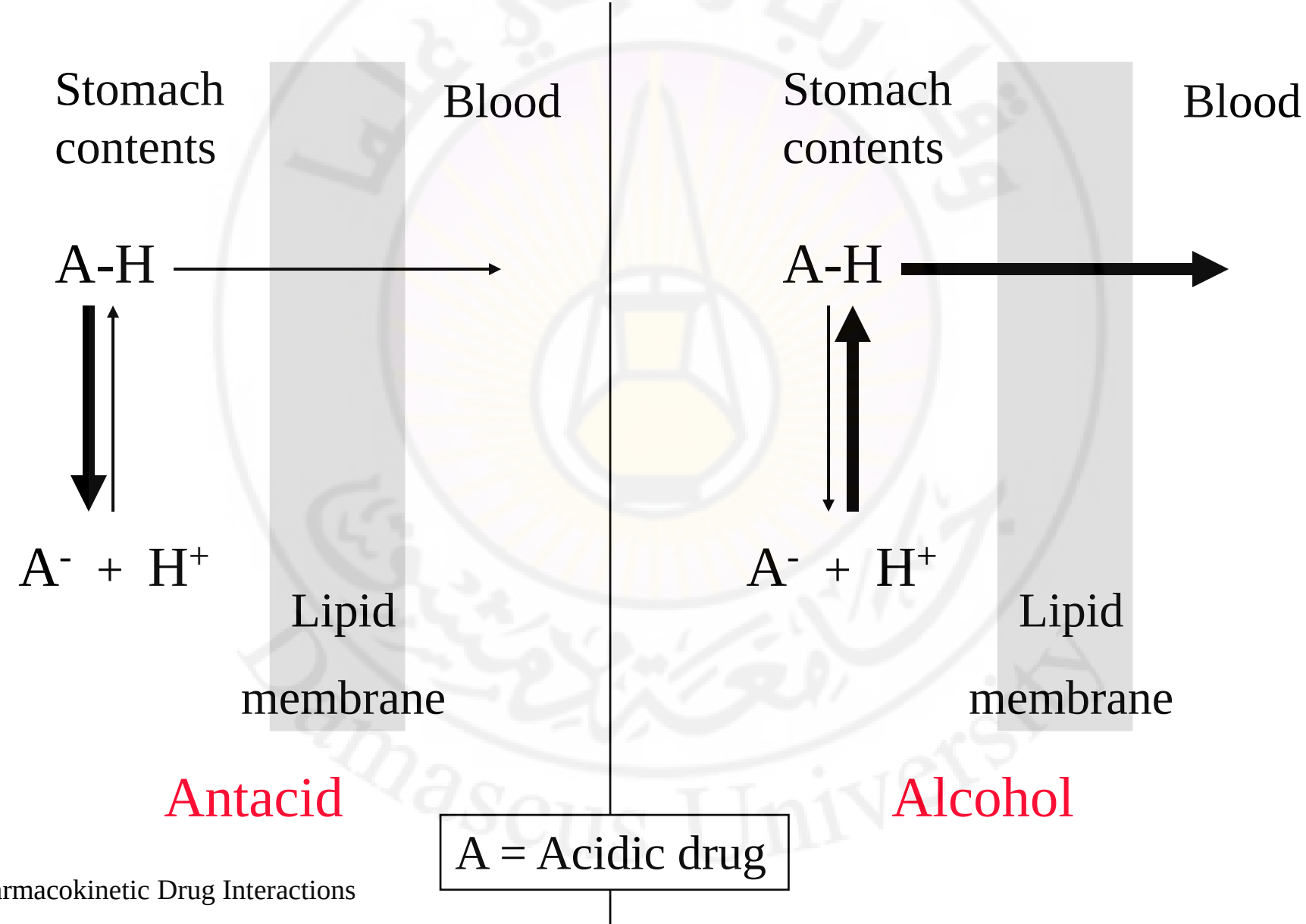
Alcohol and some foods cause acid secretion. pH ↓

Small and large intestine.

pH always near neutral.

No significant changes seen.

Alleged mechanism



Theory

Antacids

↓

Less acidic stomach contents

↓

More ionisation

↓

Slower absorption

Alcohol

↓

More acidic stomach contents

↓

Less ionisation

↓

Faster absorption

Above is for acid drug. ***Opposite pattern for a basic drug.***

Practice

- Most drug absorption occurs from the ***intestine***, not the stomach (Surface area + Blood flow).

- ***Changes in rate of absorption from the stomach are of little consequence.***

- Acidity also changes the rate of dissolution of acid drugs. Antacids make them **dissolve quicker** which cancels out (or even) exceeds the effect of **ionisation changes.**

Clinical significance

Changes in pH of G.I.T. contents

Very little (if any).

Gastric emptying and intestinal motility

Drug absorption from small intestine is much more efficient than from the stomach.

Drug A alters rate of gastric emptying.

Rate of absorption of **drug B** is also altered.

Drugs altering rate of gastric emptying

- *Opiate analgesics* (e.g. Morphine, pethidine) ***Much slower***
- *Antimuscarinic drugs* (e.g. Atropine, propantheline) ***Slower***
- *Tri-cyclic anti-depressants* - **antimuscarinic** side-effects (e.g. Imipramine) ***Slower***
- ***Muscarinic agents (e.g.* Bethanechol) *Faster***

Clinical significance
Multiple dosing

With multiple dosing:

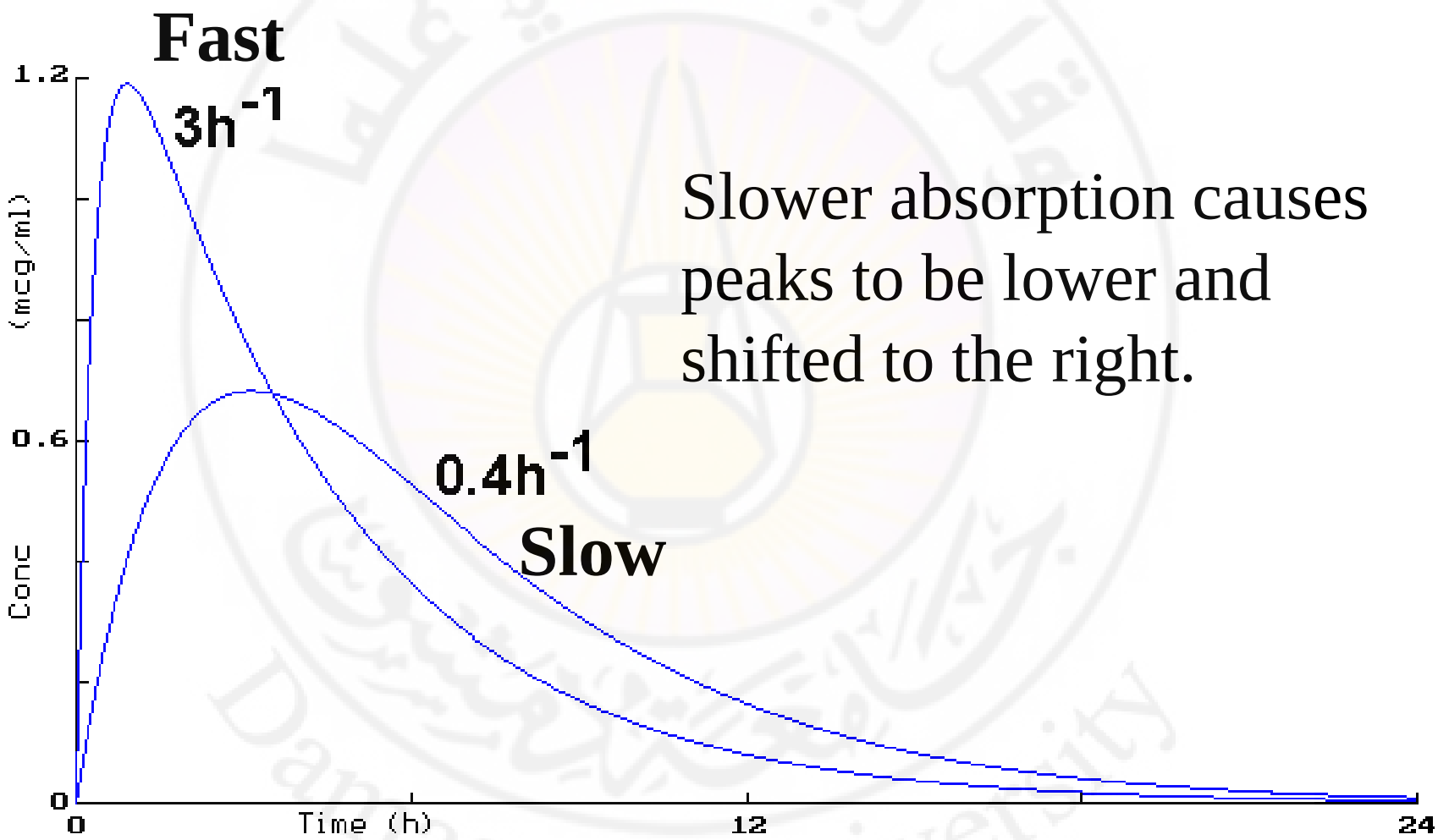
$$Css = \frac{F.Dose}{Cl.\tau}$$

Css depends upon **extent** of absorption (**F**), **not rate** (**Ka**).

Changes in gastric emptying generally affect the rate rather than the extent of drug absorption.

Not of great clinical significance.

Clinical significance, Single dose



Slower absorption causes peaks to be lower and shifted to the right.

Clinical significance

Single dose

If blood levels of the affected drug need to arise above a certain level to be effective (e.g. pain killer), a reduced rate of absorption could theoretically be significant.

Examples that would cause real clinical concern are hard to find.

Physico-chemical interactions

Two drugs bind together within the G.I.T. contents and then neither is absorbed.

Examples:

- **Tetracycline**
- **Colestyramine**
- **Charcoal**

Tetracyclines and polyvalent cations

e.g. Ca^{2+}, Al^{3+}, Mg^{2+} or Fe^{2+}
Form non-absorbable chelates with tetracyclines.

Iron tablets - Fe^{2+}
Antacids - Al^{3+}, Mg^{2+} etc
Dairy products (Milk, cheese) - Ca^{2+}

Effect is considerable. Antacids can reduce absorption of tetracyclines by 80%.

Solution: Leave a 2 hour gap between the two drugs.

Colestyramine and acidic drugs

Colestyramine: Basic anion exchange resin.

Purpose: Bind to bile acids, prevent their re-absorption, force body to synthesis new bile acids from cholesterol, reduce cholesterol load in body.

Problem: Non-selective. Binds any acidic molecule, inc. acidic drugs.

Examples: Thyroxine, valproate, thyroxine may show reduced absorption..

Charcoal

Therapeutic use rather than interaction.

Charcoal absorbs most drugs.

Used in over-doses.

Given within 1 hour of : digoxin, phenytoin, aspirin (etc) overdose, reduces absorption by up to 95%

Terms with which you should be familiar

- **Pharmacokinetic interaction**
- **Pharmacodynamic interaction**

CLASSIFICATION OF MECHANISM

ALTERATIONS IN ABSORPTION

Complexation/Chelation

Altered GI Transit

Altered Gastric pH

Example: H-2 blockers + ketoconazole

Impact: dissolution of ketoconazole is decreased, resulting in reduced absorption

CLASSIFICATION OF MECHANISM

ALTERATIONS IN ABSORPTION
ALTERATIONS IN HEPATIC METABOLISM

Induction of Metabolism

rifampin **+ theophylline**

Inhibition of Metabolism

Example: *cimetidine* + theophylline

Impact: cimetidine reduces the clearance of theophylline causing an increase in adverse effects

CLASSIFICATION OF MECHANISM

ALTERATIONS IN ABSORPTION
ALTERATIONS IN HEPATIC METABOLISM
ALTERATIONS IN RENAL CLEARANCE

Increase in Renal Blood Flow

Example: hydralazine + digoxin

Impact: hydralazine *increases* the renal clearance of digoxin

CLASSIFICATION OF MECHANISM

ALTERATIONS IN ABSORPTION
ALTERATIONS IN HEPATIC METABOLISM
ALTERATIONS IN RENAL CLEARANCE

Increase in Renal Blood Flow
Inhibition of Active Tubular Secretion

Example: probenecid + penicillin

Impact: probenecid prolongs the half-life of penicillin, allowing single dose therapy

CLASSIFICATION OF MECHANISM

ALTERATIONS IN ABSORPTION
ALTERATIONS IN HEPATIC METABOLISM
ALTERATIONS IN RENAL CLEARANCE

Increase in Renal Blood Flow
Inhibition of Active Tubular Secretion
Alterations in Tubular Reabsorption

Example: antacids + aspirin

Impact: antacids reduce the tubular reabsorption of salicylate via an increase in urine pH

FACTORS WHICH ALTER HEPATIC BLOOD FLOW

Increased Flow

- Glucagon
- Isoproterenol
- Phentolamine
- Phenobarbital
- High-protein meal
- Viral hepatitis

Decreased Flow

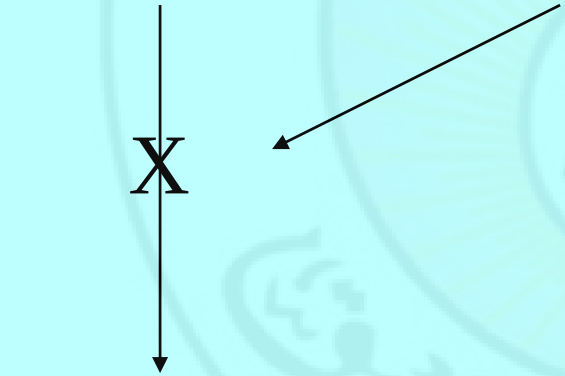
- Propranolol
- Norepinephrine
- Anesthetics
- Labetalol
- Upright posture
- Hypovolemia
- CHF
- cirrhosis

What you should be able to do

- Distinguish pharmacokinetic from pharmacodynamic interactions.
- Cite examples of drugs etc that might alter gastro-intestinal pH or motility and explain how such changes might lead to altered drug absorption
- Identify cases where one drug might bind to and prevent the absorption of another drug.
- Assess the practical clinical significance of the above theoretical interaction mechanisms.

Drug interaction

- **Parkinson :**
- L.Dopa + Carbidopa (extracerebral dopa carboxylas inhi



Drug interaction

- Antibiotics + Ethinyloestardiol ⟶ Liver
- Ethinyloestradiol conjugated
- Flora
- Oestrogen

Pharmacodynamic interactions;

It means alteration of the dug action without change in its serum concentration by pharmacokinetic factors.

EX., Propranolol + verapamil → **Synergistic or additive effect**

Synergism means =1+1=3

Additive means= 1+1=2

Potentiation means= 1+ 0=2

Antagonism means 1+1=0 or 0.5

On the other hand

Effect at the receptor site
- **Antiadrenegic**
- **anticholinergic**

Drug interactions

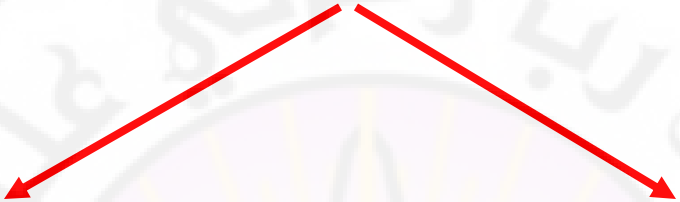
Definition;

It is the modification of the effect of one drug (the object drug) by the prior concomitant administration of another (precipitant drug).

Outcomes of drug interactions

1) **Loss of therapeutic effect**
2) **Toxicity**
3) **Unexpected increase in pharmacological activity**
4) **Beneficial effects e.g additive & potentiation (intended) or antagonism (unintended).**
5) **Chemical or physical interaction**
   e.g I.V incompatibility in fluid or syringes mixture

Mechanisms of drug interactions



Pharmacokinetics **Pharmacodynamics**

Pharmacokinitics involve the effect of a drug on another from the point of view that includes absorption ,distribution , metabolism and excretion.

Pharmacodynamics are related to the pharmacological activity of the interacting drugs
e.g synergism, antagonism, altered cellular transport, effect on the receptor site.

Pharmacokinetic interactions

1) Altered GIT absorption.

- **Altered pH, Altered bacterial flora, formation of drug chelates or complexes, drug induced mucosal damage and altered GIT motility.**

a) Altered pH;

The non-ionized form of a drug is more lipid soluble and more readily absorbed from GIT than the ionized form does.

Ex1., antiacids → Increase the pH → Decrease the tablet dissolution of Ketoconazole (acidic)

Ex2., H2 antagonists → pH ↑ → Decrease the tablet dissolution of Ketoconazole (acidic)

Therefore, these drugs must be separated by at least 2h in the time of administration of both .

b) *Altered intestinal bacterial flora ;*

EX., In 10% of patients receive digoxin…..40% or more of the administered dose is metabolized by the intestinal flora

Antibiotics kill a large number of the normal flora of the intestine → **Increase digoxin conc. and increase its toxicity**

c) Complexation or chelation;

EX1., Tetracycline interacts with iron preparations

or

Milk (Ca^{2+}) → **Unabsorpable complex**

EX2., Antacid (aluminum or magnesium) hydroxide

Decrease absorption of ciprofloxacin by 85% due to chelation

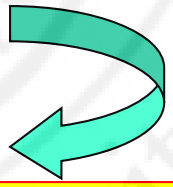
d) Drug-induced mucosal damage.

Antineoplastic agents **e.g., cyclophosphamide**
vincristine
procarbazine

Inhibit absorption of several drugs eg., digoxin

e) Altered motility

Metoclopramide (antiemitic)



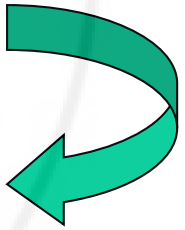
Increase absorption of cyclosporine due to the increase of stomach empting time

Increase the toxicity of cyclosporine

F) Displaced protein binding

It depends on the affinity of the drug to plasma protein.
The most likely bound drugs is capable to displace others.
The free drug is increased by displacement by another drug with higher affinity.

Phenytoin is a highly bound to plasma protein (90%), Tolbutamide (96%), and warfarin (99%)



Drugs that displace these agents are **Aspirin**
Sulfonamides
phenylbutazone

g) Altered metabolism

The effect of one drug on the metabolism of the other is well documented. The liver is the major site of drug metabolism but other organs can also do e.g., WBC,skin,lung, and GIT.

CYP450 family is the major metabolizing enzyme in phase I (oxidation process).

Therefore, the effect of drugs on the rate of metabolism of others can involve the following examples.

EX1., Enzyme induction

A drug may induce the enzyme that is responsible for the metabolism of another drug or even itself e.g.,

Carbamazepine (antiepileptic drug) increases its own metabolism

Phenytoin increases hepatic metabolism of theophylline Leading to decrease its level ⟶ Reduces its action

and

Vice versa

N.B enzyme induction involves protein synthesis .Therefore, it needs time up to 3 weeks to reach a maximal effect

EX2., Enzyme inhibition;

It is the decrease of the rate of metabolism of a drug by another one.This will lead to the increase of the concentration of the target drug and leading to the increase of its toxicity .

Inhibition of the enzyme may be due to the competition on its binding sites , so the onset of action is short may be within 24h.

N.B; When an enzyme inducer (e.g.carbamazepine) is administered with an inhibitor (verapamil) ⟶

The effect of the inhibitor will be predominant

Ex.,Erythromycin inhibit metabolism of *astemizole and terfenadine*

Increase the serum conc. leading to increasing the life threatening cardiotoxicity

EX., Omeprazole → **Inhibits oxidative metabolism** → **of diazepam**

First-pass metabolism:

Oral administration increases the chance for liver and GIT metabolism of drugs leading to the loss of a part of the drug dose decreasing its action. This is more clear when such drug is an enzyme inducer or inhibitor.

EX., Rifampin lowers serum con. of verapamil level by increase its first pass . Also, Rifampin induces the hepatic metabolism of verapamil

Renal excretion:

- **Active tubular secretion;**

  It occurs in the proximal tubules (a portion of renal tubules). The drug combines with a specific protein to pass through the proximal tubules.

When a drug has a competitive reactivity to the protein that is responsible for active transport of another drug .This will reduce such a drug excretion increasing its con. and hence its toxicity.

EX., Probenecid ….. ⟶ Decreases tubular secretion of methotrexate.

* Passive tubular reabsorption;

Excretion and reabsorption of drugs occur in the tubules By passive diffusion which is regulated by concentration and lipid solubility.

N.B., Ionized drugs are reabsorbed lower than non-ionized ones

Ex1., Sod.bicarb. → **Increases lithium clearance and decreases its action**

Ex2., Antacids → **Increases salicylates clearance and decreases its action**

Pharmacodynamic interactions;

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* Risk factors:

1) *High risk drugs;* these are the drugs that show a narrow therapeutic index e.g., corticosteroids, rifampin, oral contraceptives, quindine, lidoquine and theophyllin

2) *High risk patients;* these are the groups of patients that should be treated with caution due to a specific heath condition e.g., pregnant women, malignant cases, diabetic patients, patients with liver or kidney disorders asthmatic patients and cardiac disorders.

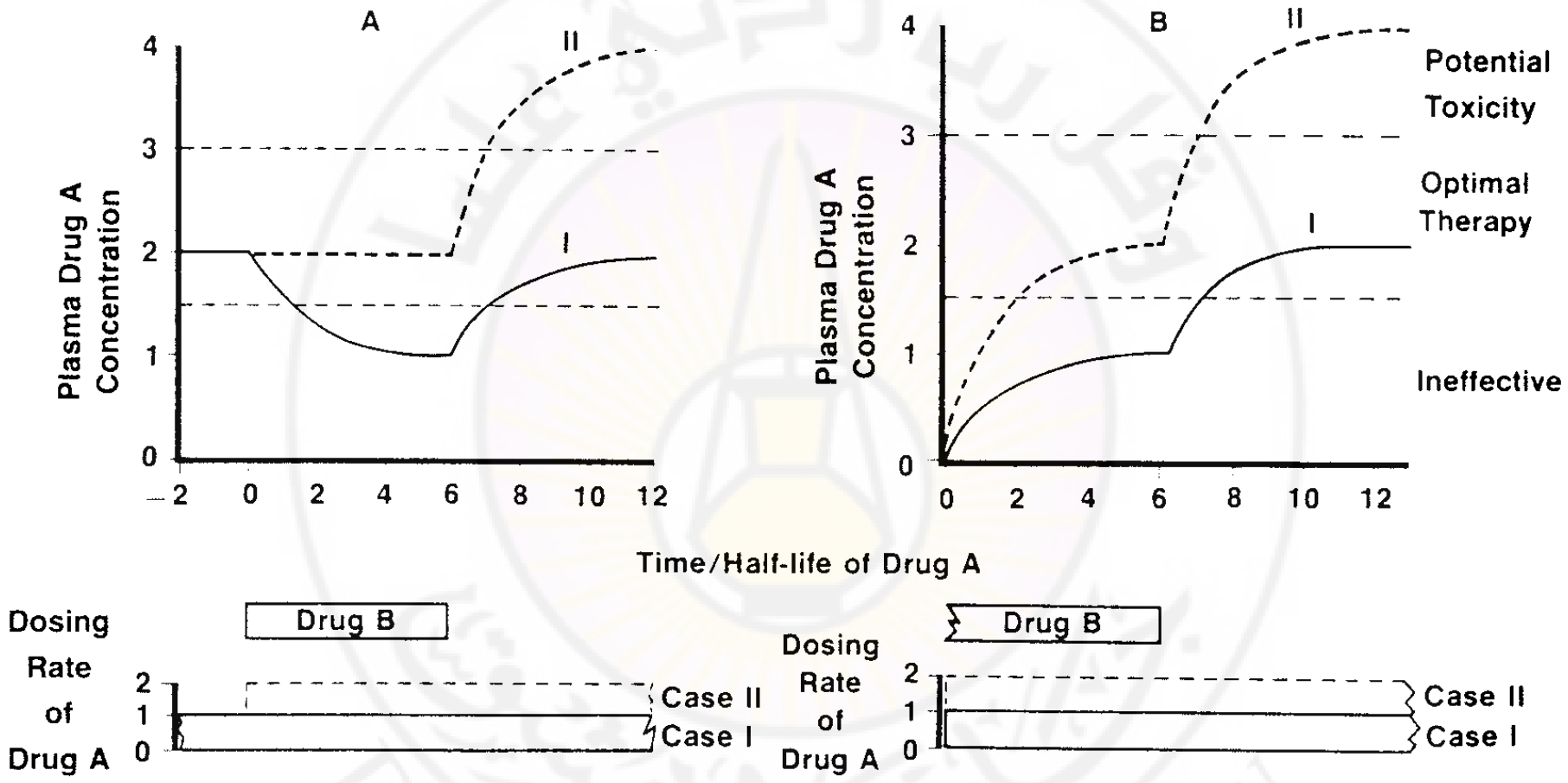
•Onset of drug interaction

It may be seconds up to weeks for example in case of enzyme induction, it needs weeks for protein synthesis, while enzyme inhibition occurs rapidly.

The onset of action of a drug may be affected by the half lives of the drugs e.g., cimitidine inhibits metabolism of theophylline.

Cimitidine has a long half life, while, theophylline has a short one.

When cimitidine is administered to a patient regimen for Theophylline, interaction takes place in one day.


A
II
I
Plasma Drug A Concentration
4
3
2
1
0
−2
0
2
4
6
8
10
12
B
II
I
Potential Toxicity
Optimal Therapy
Ineffective
Plasma Drug A Concentration
Time/Half-life of Drug A
Dosing Rate of Drug A
Drug B
Case II
Case I
2
1
0
Dosing Rate of Drug A
Drug B
Case II
Case I

III. ALTERATIONS IN DRUG METABOLISM

A. Induction

$$E_H = \frac{f_{ub} CL_{u\,\mathrm{int}}}{Q_H + f_{ub} CL_{u\,\mathrm{int}}}$$

$$CL_H = \frac{Q_H f_{ub} CL_{u\,\mathrm{int}}}{Q_H + f_{ub} CL_{u\,\mathrm{int}}}$$

$$AUC_O = \frac{F \times Dose}{f_{ub} CL_{u\,\mathrm{int}}}$$

$$F = \frac{Q_H}{Q_H + f_{ub} CL_{u\,\mathrm{int}}}$$

* Prevention of drug interaction

1) **Monitoring therapy and making adjustments**

2) **Monitoring blood level of some drugs with narrow therapeutic index e.g., digoxin, anticancer agents…etc**

3) **Monitoring some parameters that may help to characterize the the early events of interaction or toxicity e.g., with warffarin administration, it is recommended to monitor the prothrombin time to detect any change in the drug activity.**

4) **Increase the interest of case report studies to report different possibilities of drug interaction**

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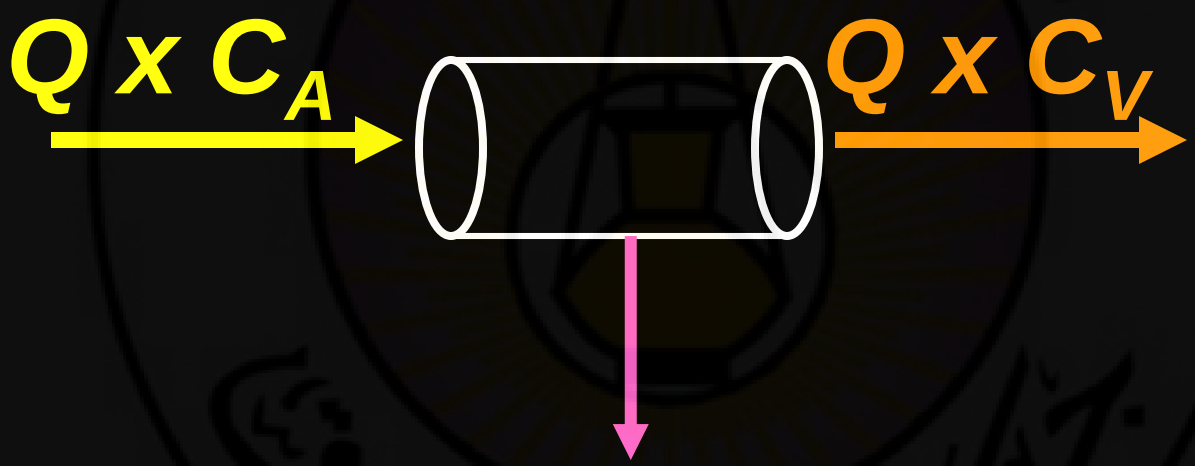
HEPATIC CLEARANCE

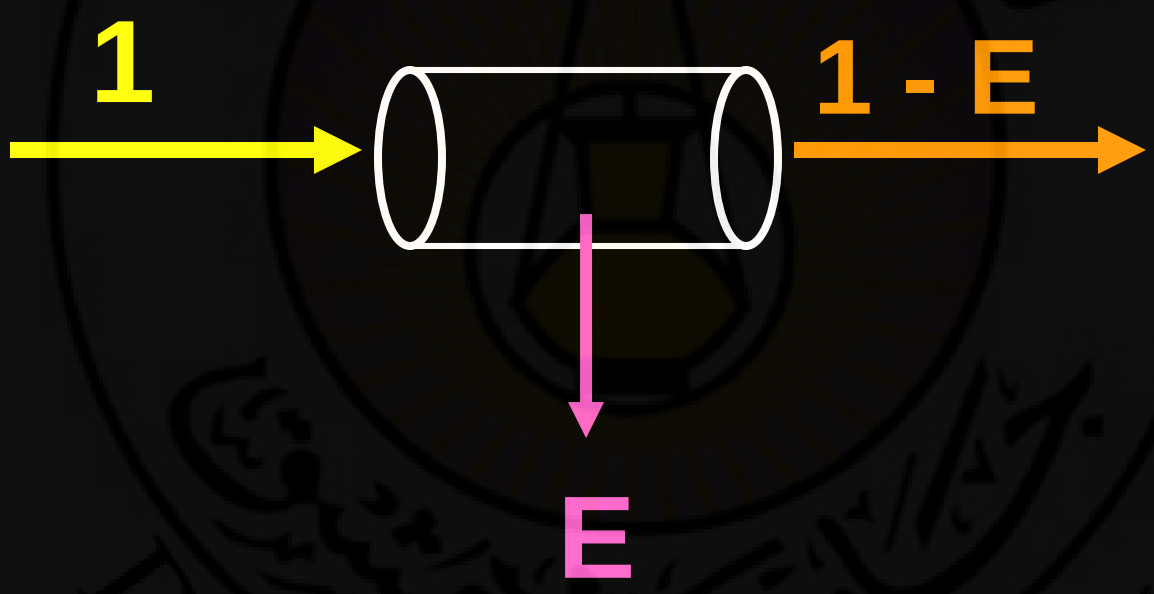
1. Mass Balance



Rate of Extraction

HEPATIC CLEARANCE

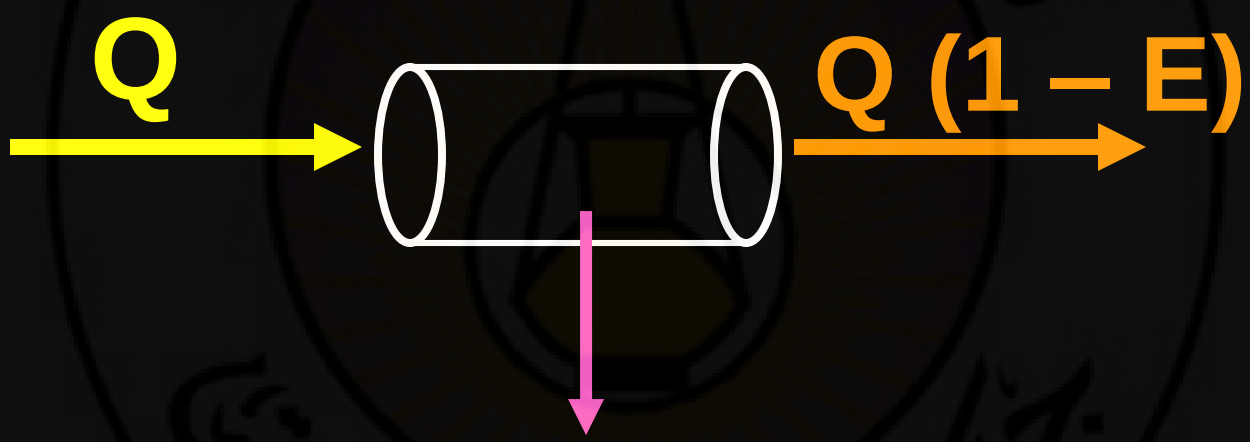
2. Mass Balance Normalized to Rate of Entry



Extraction Ratio

HEPATIC CLEARANCE

3. Mass Balance Normalized to C_A



Clearance

III. ALTERATIONS IN DRUG METABOLISM

A. Induction

$$E_H = \frac{f_{ub} CL_{u\,\mathrm{int}}}{Q_H + f_{ub} CL_{u\,\mathrm{int}}}$$

$$CL_H = \frac{Q_H f_{ub} CL_{u\,\mathrm{int}}}{Q_H + f_{ub} CL_{u\,\mathrm{int}}}$$

$$AUC = \frac{F \times Dose}{f_{ub} CL_{u\,\mathrm{int}}}$$

$$F = \frac{Q_H}{Q_H + f_{ub} CL_{\mathbf{uint}}}$$

$$CL_H \equiv Q_H E$$

Suggests that

$$CL_H \sim Q_H$$

Actually

$$\uparrow Q_H = \downarrow E$$

HEPATIC EXTRACTION RATIO OF REPRESENTATIVE DRUGS

Low (<0.3)

- Antipyrine
- Diazepam
- Phenylbutazone
- Theophylline
- Tolbutamide
- Warfarin

High (>0.7)

- Lidocaine
- Meperidine
- Propoxyphene
- Propranolol
- Verapamil

Intermediate: Quinidine

$$CL_H = \frac{Q_H \times f_{ub} CL_{u\,\mathrm{int}}}{Q_H + f_{ub} CL_{u\,\mathrm{int}}}$$

When $Q_H >> f_{ub} CL_{u\,\mathrm{int}}$, then $CL_H \cong f_{ub} CL_{u\,\mathrm{int}}$

When $Q_H << f_{ub} CL_{u\,\mathrm{int}}$, then $CL_H \cong Q_H$

Consider a low clearance drug iv:

CL_{uint} = 0.25 L/min Q_H = 1.5 L/min

f_{ub} = 0.1 R_0 = 0.25 mg/min

$$CL_H = \frac{Q_H \times f_{ub} CL_{u\,\mathrm{int}}}{Q_H + f_{ub} CL_{u\,\mathrm{int}}}$$

$$CL_H = \frac{1.5\ \mathrm{L/min} \times 0.1 \times 0.25\ \mathrm{L/min}}{1.5\ \mathrm{L/min} + (0.1 \times 0.25\ \mathrm{L/min})}$$

$$CL_H = 0.0246\ \mathrm{L/min}$$

What if f_{ub} = 0.2?

$$CL_H^* = \frac{Q_H \times f_{ub}^* CL_{u\,\mathrm{int}}}{Q_H + f_{ub}^* CL_{u\,\mathrm{int}}}$$

$$CL_H^* = \frac{1.5\ \mathrm{L/min} \times 0.2 \times 0.25\ \mathrm{L/min}}{1.5\ \mathrm{L/min} + (0.2 \times 0.25\ \mathrm{L/min})}$$

$$CL_H^* = 0.0484\ \mathrm{L/min}$$

What about oral administration?

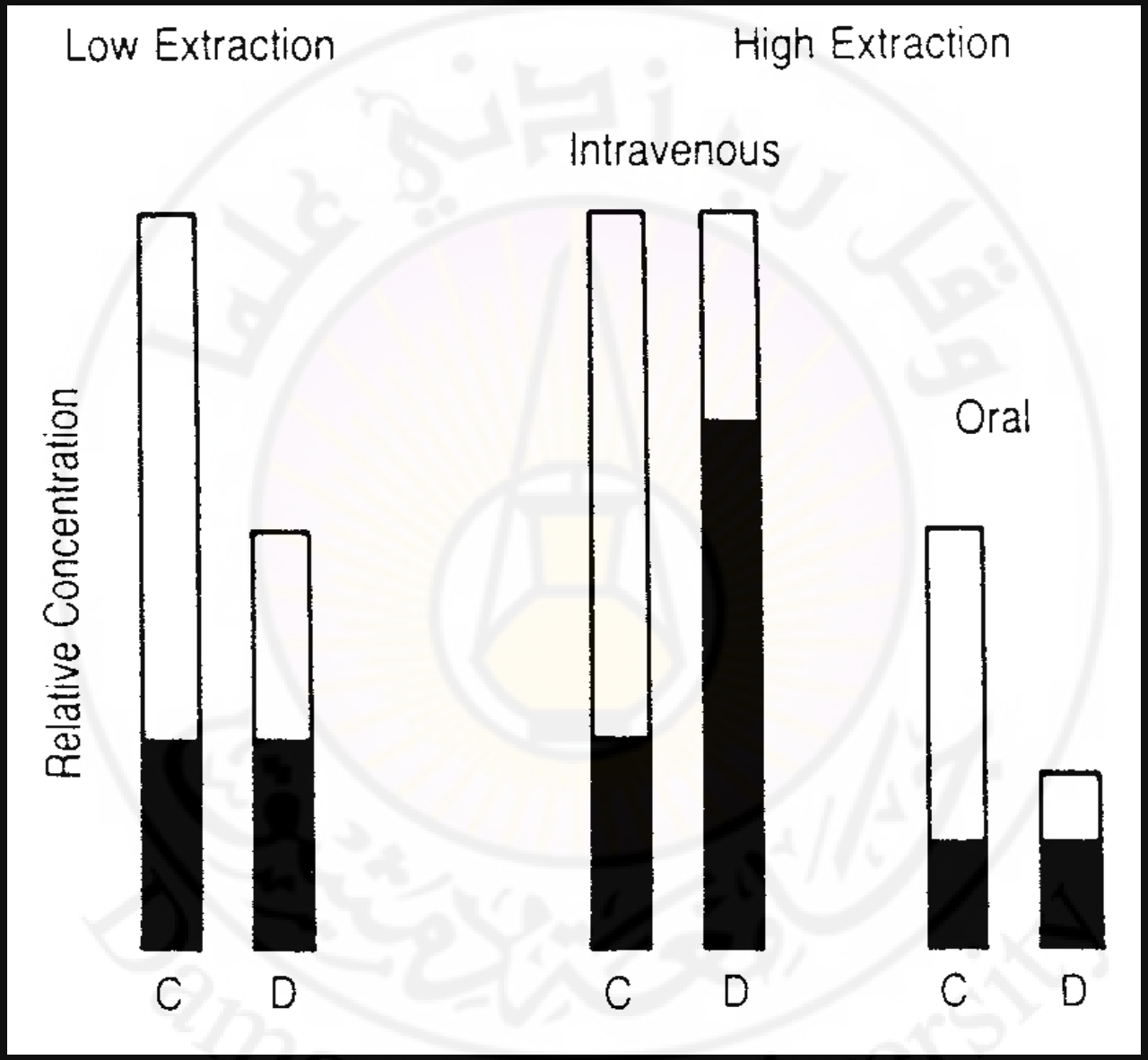
$$F = 1 - \frac{f_{ub} CL_{u\,\mathrm{int}}}{Q_H + f_{ub} CL_{u\,\mathrm{int}}}$$

$$F = 1 - \frac{0.1 \times 0.25\ \mathrm{L/min}}{1.5\ \mathrm{L/min} + (0.1 \times 0.25\ \mathrm{L/min})}$$

$$F = 0.98$$

$$F^* = 1 - \frac{0.2 \times 0.25\ \mathrm{L/min}}{1.5\ \mathrm{L/min} + (0.2 \times 0.25\ \mathrm{L/min})}$$

$$F^* = 0.97$$



From: Rowland M, Tozer TN. *Clinical Pharmacokinetics – Concepts and Applications*, 3rd edition

E	Q_H	f_{ub}	f_{ut}	CL_T	V_{ss}	$t_{1/2}$	F
High	↑	⇔	⇔				
Low	↑	⇔	⇔				

CL = 420 ml/in, Fu = 0.5, Fe = 0.7

Administration with competitive inhibitor renal secration

Cl = V= T1/2=

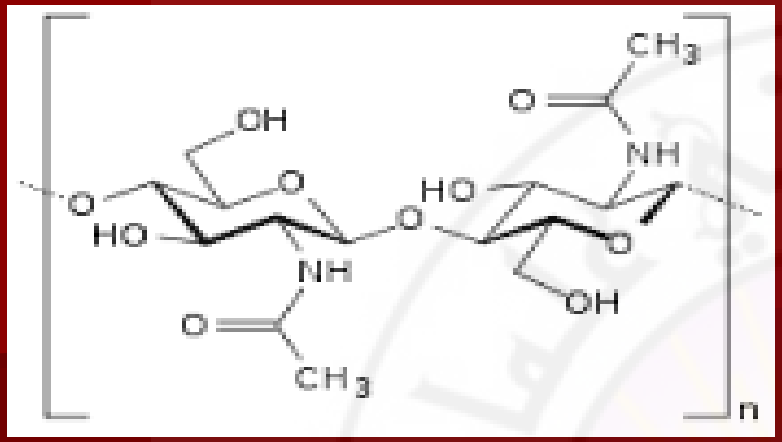
Fe = F=

Antifungal Drugs

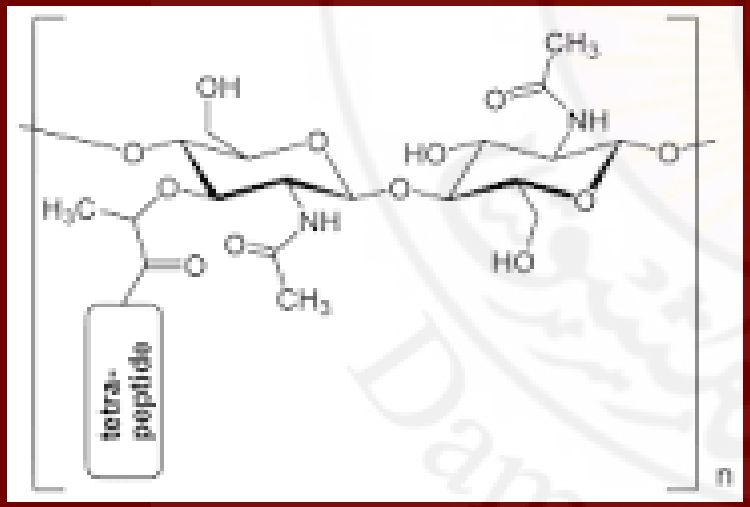
- **Overview**
- **Infectious diseases** caused by **fungi** are ***called mycoses***, and they are often **chronic** in nature. Many common mycotic infections are **superficial** and only involve the **skin** (**cutaneous** mycoses), but fungi may also penetrate the skin, causing ***subcutaneous*** infections. **The fungal infections that are most difficult to treat are the *systemic mycoses*, which are often life-threatening.**

- ***Unlike bacteria***, ***fungi cell walls*** composed largely of ***chitin*** a polymer of ***N-acetylglucosamine*** rather than **peptidoglycan** (a characteristic component of most **bacterial cell walls**).

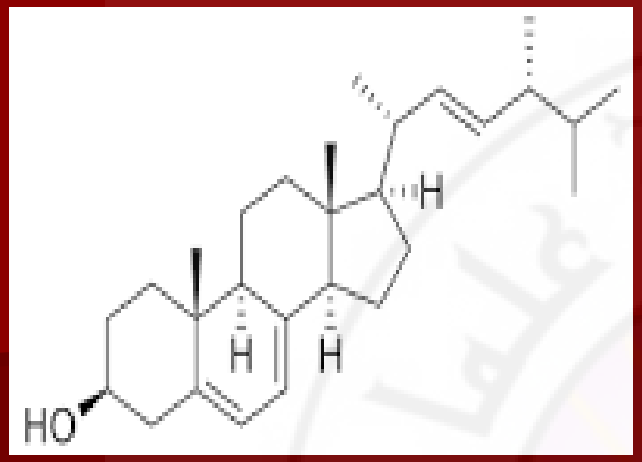
- The ***fungal cell membrane*** contains ***ergosterol*** rather than the **cholesterol** found in **mammalian membranes**. These chemical characteristics are useful in targeting chemotherapeutic agents against fungal infections.



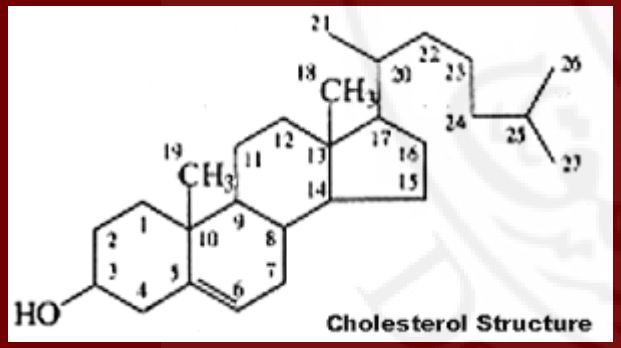
- **(C8H13O5N)n = Hexosamines = CHITIN**



- **Peptidoglycan**



- ***ergosterol***



- **cholesterol**

- **Fungal infections** are generally **resistant to antibiotics** used in the treatment of bacterial infections, and **conversely**, **bacteria are resistant to the antifungal agents**. The last two decades have seen a rise in the incidence of fungal infections so that **candidemia** is the fourth most common cause of **septicemia.**

- **Mycoses** can be further defined into fungi that are **yeasts or molds.**
- The terms ***yeast form*** **reproduce by budding (** التبرعم**).**
- **Yeasts include , Examp:** ***Candida*** **,** ***Cryptococcus*** المُسْتَخْفِيَةُ ….,. The pathogenic species of *Candida* include ***C. albicans,*** *C. krusei*, *C. parapsilosis*, ***C. tropicalis,*** *C. lusitaniae*, *C. glabrata* (*Torulopsis glabrata*), *C. guilliermondii*, *C. pseudotropicalis*, and *C. dubliniensis*.

- **Molds are composed of hyphae (خيط).**
- **Molds** include **Aspergillus** and the agents of **mucormycosis** فُطَار عَفَنِيّ.
- ***Aspergillus fumigatus*** is the **most pathogenic** of the **molds** and the most common of that species to cause invasive disease.
- **Other species of aspergillus include *A. flavus*, *A. terreus*, and *A. niger*.**

- The **dimorphic** fungi are capable of producing both **hyphal** and **yeast like** forms **depending on temperature.**
- They typically grow as **yeasts at body temperature** and as ***molds at room temperature.***
- The **dimorphic** fungi include the agents of **histoplasmosis, blastomycosis, sporotrichosis** داءُ الشَّعْرِيَّاتِ المُبَوَّغَة , **coccidiomycosis, paracoccidioidomycosis, and chromoblastomycosis** فُطارُ اصْطِباغِيّ
-

- This **increased** incidence of **fungal infections** is associated with greater numbers of individuals who are **on :**
- **Chronic immune suppression following organ transplant,**
- **Undergoing chemotherapy for myelogenous and solid tumors**, or
- **Infected with the human immunodeficiency virus (HIV).**

- **The five major pathogens that cause endemic mycoses are :**
- **(1)** ***Coccidioides immitis,*** الكُرَوانِيَّةُ اللَّدودَة
- **(2)** ***Histoplasma capsulatum,*** النَّوسَجَةُ المُغَمَّدَةُ
- **(3)** ***Blastomyces dermatitidis*** البُرْعُمِيَّةُ المُلْهِبَةُ للجِلْد
- **(4) Aspergillosis** الرشاشيات
- **(5) Candidiasis** المبيضات

- ANTIFUNGAL DRUGS
- 1- SUBCUTANEOUS & SYSTEMIC MYCOSES
- Amphotericin B
- Flucytosine
- Ketoconazole
- Fluconazole
- Itraconazole
- Voriconazole
- Posaconazole
- Echinocandins : Caspofungin, micafungin, and anidulafungin.

- **ANTIFUNGAL DRUGS**
- **2- CUTANEOUS MYCOSES**
- Naftifine
- Griseofulvin
- **Nystatin**
- Miconazole
- Clotrimazole
- Butoconazole
- Terconazole
- Econazole.

Aspergillosis

Aspergillosis, the most common invasive mold infection worldwide, caused by Approximately 150 species include *A. fumigatus, A. flavus, A. niger,* *A. terreus*, and *A. nidulans*. *A. fumigatus is* the predominant species causing invasive aspergillosis. *A. fumigatus* is the *most rapidly growing* species and *has very small spore size,* allowing *deep penetration into the lungs.*

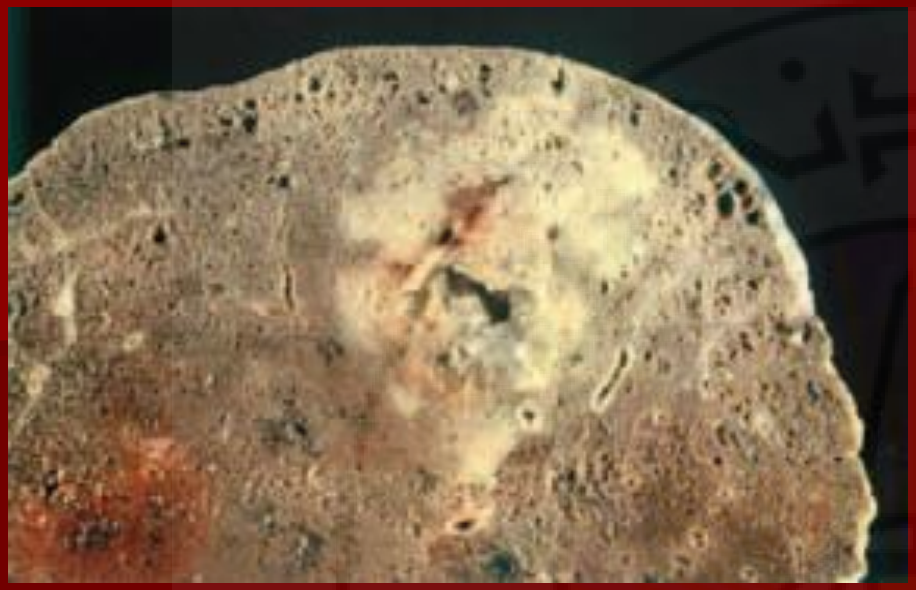
Macrophage and neutrophils are the primary host defenses against *Aspergillus* in the lungs.

Corticosteroids can substantially impair the functions of macrophages and neutrophils.

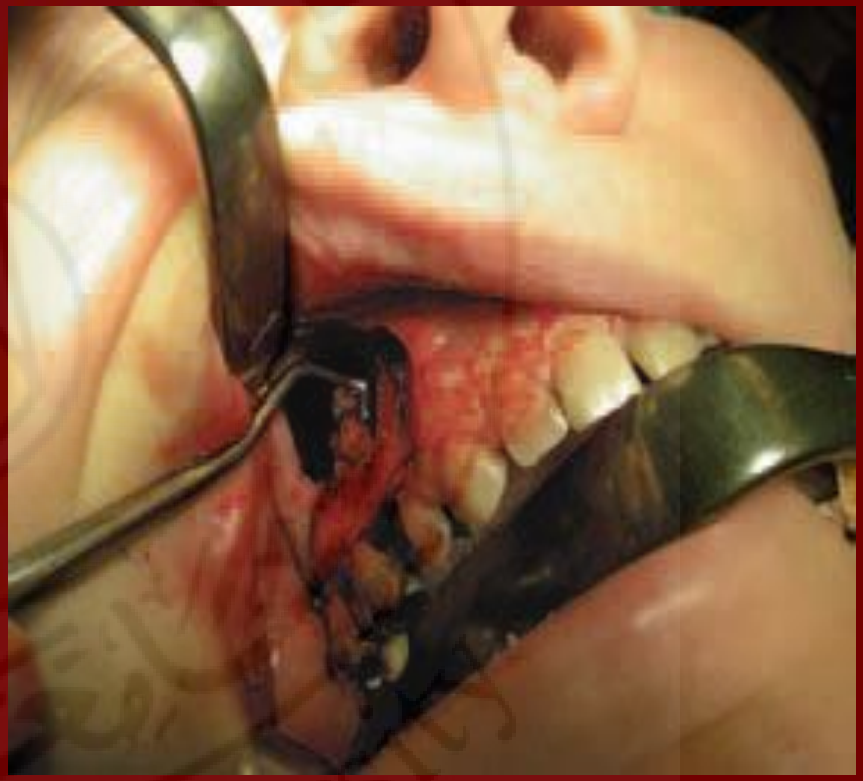
T-cell function is thought to be important in the more chronic forms of invasive aspergillosis.

- **Acute Pulmonary**
- Acute invasive pulmonary aspergillosis occurs primarily in immunocompromised hosts. Early symptoms may consist of dry cough with fever and nonspecific chest pain. Hemoptysis can occur with focal disease without warning and can be life threatening. More commonly, the clinical presentation of acute pulmonary aspergillosis in *immunocompromised hosts* is one of *unremitting fever* and the development of *lung infiltrates* despite broad-spectrum antibacterial therapy.

- **Chronic Pulmonary**
- **Chronic invasive aspergillosis occurs less frequently than acute aspergillosis. Affected patients commonly have underlying conditions such as AIDS, chronic granulomatous disease, diabetes mellitus, alcoholism, and corticosteroid use.**
- **They include chronic productive cough, mild to moderate hemoptysis, low-grade fever, malaise, and weight loss.**



Invasive aspergillosis of the lung



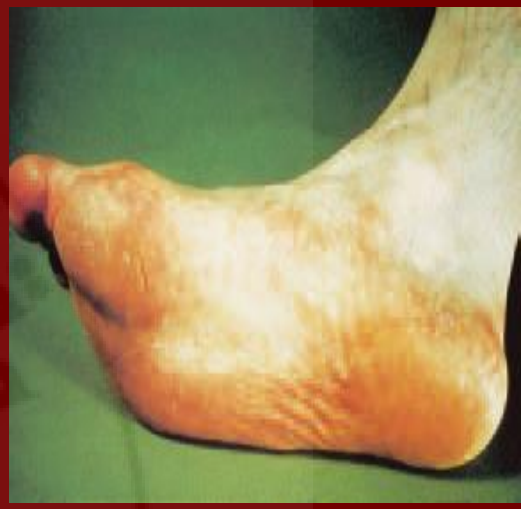
Aspergilloma in the maxillary sinus

Management

- **Acute invasive pulmonary aspergillosis**
- • **Amphotericin B:** 1.0–1.5 mg/kg/day, to a total dose of at least 25 mg/kg (1 month) (DW5%).
- • **Itraconazole: 600 mg/day for 4-7 days** then **200 mg twice daily (3 months).**
- • **Caspofungin:** 70 mg/day until patient stabilizes.
- • **Voriconazole: 6 mg/kg, IV b.i.d. on day 1** followed by **4 mg/kg,IV b.i.d. until patient stabilizes**, **then 200 mg/day, b.i.d, orally.**

Dermatophytosis
Tinea pedis سعفة القدم

Interdigital tinea pedis due to *Trichophyton rubrum*.



Moccasin form of tinea pedis.

Definition

Dermatophyte infection of the feet.

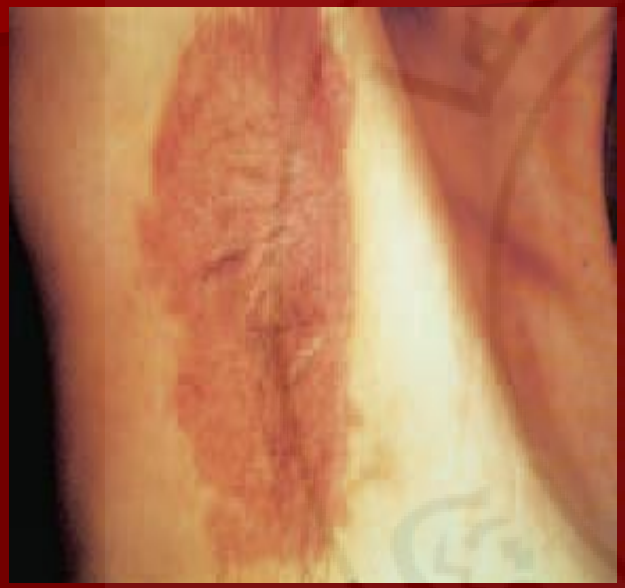
Causal organisms and habitat

- ***Trichophyton rubrum*** الشَّعْرَوِيَّةُ الحَمْراء is the most common cause.

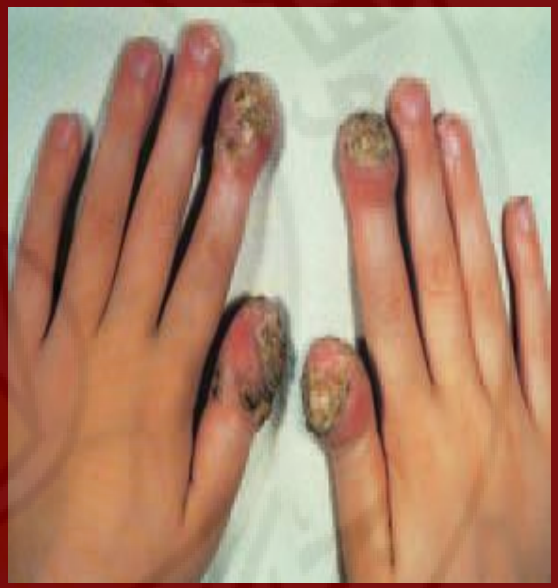
- **Management**
- This condition seldom resolves if untreated. However, it often responds to :
- **Topical treatment : with an azole (clotrimazole, econazole, miconazole, sulconazole), naftifine or terbinafine morning and evening for 2–4 weeks.**
- **Oral therapy**, if indicated, includes these alternatives:
- • **itraconazole:** 200 – 400 mg/day for 1 week.
- • **terbinafine:** 250 mg/day for 2– 6 weeks.

- **Cutaneous candidosis, Definition**
- Cutaneous candidosis is a ***yeast*** infection of the skin caused by members of the genus ***Candida***. Infection of the proximal nail fold known as ***Candida paronychia*** داحِس
- (التهاب ما حول الظفر) may lead to nail infection.
- **Causal organisms and habitat**
- • Most commonly caused by *Candida albicans* then *C. tropicalis* ; other species are occasionally implicated: Normal flora of the **skin, mouth, intestinal tract and vagina**.

- **Mucosal and cutaneous infections**
- **Cutaneous candidosis**

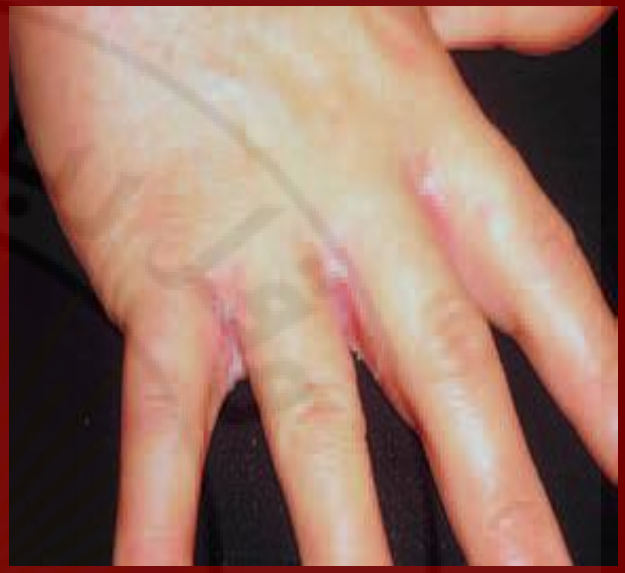


Candida *albicans* infection of axilla.

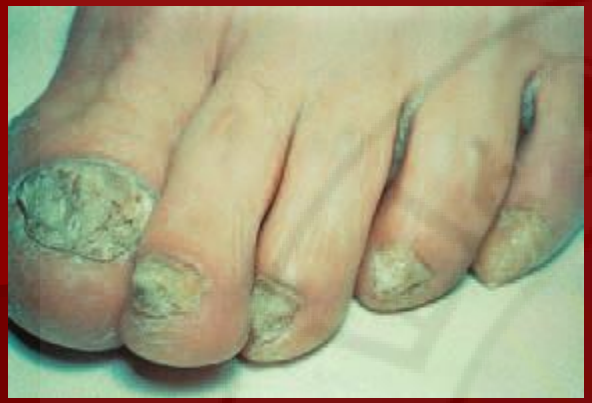


Chronic mucocutaneous **candidosis**.

Candida granuloma of the forehead and angular cheilitis associated with chronic mucocutaneous candidosis due to congenital defects in cell-mediated immunity.

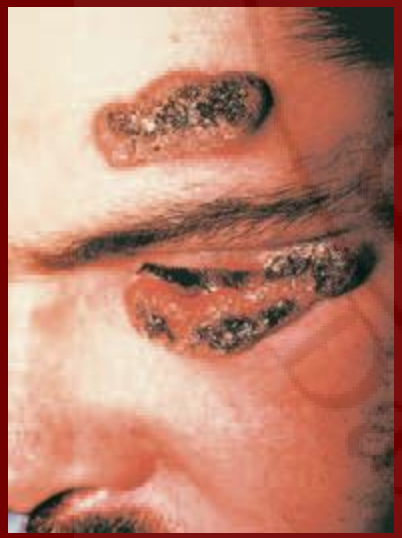


Interdigital candidosis caused by *Candida albicans*.



Tinea unguium due to *Trichophyton rubrum*

Superficial white onchomycosis.



Cutaneous blastomycosis

Chronic cutaneous coccidioidomycosis showing granulomatous lesions on face, neck and chin.

- **Management:**
- **Topical therapy:** with **azole** agents, **nystatin** and **naftifine**, should be **used twice daily until 1–2 weeks after clearing.**
- **Oral agents:** are indicated for folliculitis, nail involvement, extensive lesions and in the immunocompromised:
- ● **itraconazole 200 mg/day or fluconazole 100 mg/day, 2-4 weeks.**

Additional steroid or antibacterial therapy may be indicated.

- ***General Treatment Guidelines***
- **1. Polyene antifungals : Amphotericin B, Nystatin, Natamycin and rimocidin**
- **2. Azoles : Imidazole, triazole, thiazole**
- **2.1 Imidazoles : Clotrimazol, Econazol, Ketoconazol, Sertaconazol, Omoconazol and Oxiconazol**

  2.2 Triazoles: Fluconazol, Itraconazol, Posaconazol, Voriconazol and Terconazol

  2.3 Thiazoles : Abafangin

General Treatment Guidelines

- **3. Allylamines : Amorolifin, Naftifine and Terbinafine**
- **4. Echinocandins : Micafungin, Caspofungin, Anidulafungin**
- **5. Others : Grisofulvin, Benzoic Acid, Flucytosine.**

The *first three antifungal* classes target *fungal cell membranes* by interacting with or *inhibiting ergosterol*.

The echinocandins uniquely target *fungal cell wall* (by inhibiting 1,3-β-D-glucan synthesis for the fungal **cell wall), chitin .**

- **Amphotericin B**
- In spite of its **toxic potential**, amphotericin B is the **drug of choice for the treatment of life-threatening, systemic mycoses**. **[**Note: **Conventional amphotericin (amphotericin B deoxycholate,** the non lipid formulation) has undergone several formulation improvements to reduce the incidence of side effects, **particularly nephrotoxicity.]** The drug is also sometimes used in **combination** with **flucytosine** so that lower (**less toxic**) levels of amphotericin B are possible.

- Antifungal spectrum: Amphotericin B is either **fungicidal or fungistatic**, **depending on: the organism *and the* concentration of the drug**. It is effective **against** a wide range of fungi, including **Candida albicans, Histoplasma capsulatum, Cryptococcus neoformans, Coccidioides immitis, Blastomyces dermatitidis and Moderate or severe aspergillosis.**
- **Resistance: Fungal resistance, although infrequent, is associated with decreased ergosterol content of the fungal membrane.**

- **Pharmacokinetics:** Amphotericin B is administered by **slow, intravenous infusion**. Amphotericin B is ***insoluble*** in water, and ***injectable preparations require the addition of sodium deoxycholate***, which produces a ***soluble colloidal dispersion***.

- The simplest and smallest of the liposome preparations, AmBisome®,.
- These **liposomal** preparations **have the primary advantage of reduced renal and infusion toxicity.**

- Amphotericin B is **extensively bound to plasma proteins** and is **distributed throughout the body, becoming highly tissue bound**.
- **Amphotericin B does cross the placenta.**
- **Amphotericin B is <u>Poorly</u> crossing BBB.**
- **Blood-Brain Barrier (BBB).**
- **Metabolized in liver.**
- **Terminal half-life of up to 15 days.**

- **Dosage adjustment is not required in** patients with **compromised hepatic function**, ***but when renal dysfunction*** **is due to the use of conventional amphotericin B, the total daily** ***dose is decreased by 50% .***

- **Adverse reactions: Amphotericin B has a low therapeutic index.**
- **A total adult daily dose should not exceed 1.5 mg/kg**. Small test doses are usually administered to assess the degree of a patient's negative responses, **such as anaphylaxis or convulsions.**
  Other toxic manifestations include the following:

- **Fever and chills: Premedication** with a **corticosteroid or an antipyretic** helps to prevent this problem.
- **Renal impairment:** Despite the low levels of the drug excreted in the urine, patients may exhibit a **decrease in GFR and renal tubular function. Creatinine clearance can drop, and *potassium and magnesium are lost.***
- ***Azotemia*:** (elevated blood urea) is **exacerbated** by other **nephrotoxic drugs, *such as*** *aminoglycosides, cyclosporine, or pentamidine,* **although adequate hydration can decrease its severity.**

- **Hypotension: accompanied by hypokalemia, *requiring potassium supplementation.* Care** must be exercised **in patients taking digoxin.**

- **Anemia:** This may be exacerbated in **patients infected with HIV who are taking zidovudine.**

- **Thrombophlebitis (التهاب الوريد الخثري):** Adding **heparin** to the infusion can **alleviate** this problem.

- **Interactions**
- **Flucytosine : Toxicity of flucytosine is increased** and allows a lower dose of amphotericin B. **Amphotericin B may also facilitate entry of flucystosine into the fungal cell.**
- **Diuretics or cisplatin : Increased renal toxicity and increased risk of hypokalemia**
- **Corticosteroids : Increased risk of hypokalemia.**

- **Interactions**
- **Aminoglycosides : Increased risk of serious renal damage**, monitor kidney function closely.
- **Ganciclovir, Tenofovir, and Adefovir :**
- **hematological** and **renal** side-effects **of amphotericin B are increased.**
- **Transfusion of leukocytes :** Risk of **pulmonale damage occurs**. Space the intervals between the application of amphotericin B and the transfusion, and monitor pulmonary function.

- **Azole = Imidazole = Ketoconazole**
- ***First orally active azole*** available for the ***treatment of systemic mycosis.***
- **Mechanism of action**: Fungistatic.
- They **inhibit C-14 α-demethylase** , thus **blocking** the **demethylation** of **lanosterol** to **ergosterol** the principal **sterol of fungal membranes.**

- **Antifungal spectrum**: Ketoconazole is active against many fungi, including : **Histoplasma, Blastomyces, Candida, and Coccidioides**, ***but not aspergillus species.***
- **Resistance**: This **is** becoming a significant **clinical problem**, particularly in the protracted therapy required for those **with** advanced **HIV infection.**

- **Pharmacokinetics:**
- **Only orally.** It requires **gastric acid** for dissolution and is **absorbed through the gastric mucosa.**
- **Administering acidifying agents, such as cola drinks, before taking the drug can improve absorption in patients with achlorhydria**.
- It is **extensively bound to plasma proteins**.
- **Penetration into tissues is limited.**
- **It *does not enter the CSF*.**
- **Extensive metabolism** occurs in the **liver,** and **excretion** is primarily through the **bile.**

- **Adverse effects**:
- In addition to **allergies**, **dose-dependent gastrointestinal disturbances**, including **nausea, anorexia, abdominal pain and vomiting**, are the most common adverse effects of ketoconazole treatment.
- ***Dose reductions*** should be considered in patients ***with severe liver disease.***

- **Drug interactions and contraindications:**
- **By inhibiting CYP3A4, CYP1A2, CYP2C9 ketoconazole** can **potentiate** the **toxicities** of **drugs** such as:
- **cyclosporine, phenytoin, tolbutamide, Buspirone, Calcium channel blockers, glimepiride, glipizide, losartan, montelukast, nateglinide, warfarin, zafirlukast and warfarin, Sildenafil, Tadalafil.**

- **Drug interactions and contraindications:**
- **Rifampin**, an **inducer** of CYP450 system, can **shorten** the **duration** of **action** of **ketoconazole and the other azoles.**
- **CONTRAINDICATIONS :** co administration with **ergot** derivatives or **cisapride** is contraindicated due to risk of **potentially fatal cardiac arrhythmias.**

Ketoconazole and amphotericin B should not be used together, because the decrease in ergosterol in the fungal membrane reduces the fungicidal action of amphotericin B **.**

Finally, ketoconazole is **teratogenic** in animals, **and it should not be given during pregnancy (C).**

DOSAGE FORMS

- **Aerosol, topical [foam] : 2% (50 g, 100 g)**
- **Cream, topical : 2% (15 g, 30 g, 60 g)**
- **Gel, topical : 2% (15 g) [contains dehydrated alcohol 34%]**
- **Shampoo, topical: 1% (120 mL), 2% (120 mL)**
- **Tablet : 200 mg (LFTs monitoring)**

- **Azole = Triazole = Fluconazole**
- **Fluconazole** is ***clinically important*** because of its **lack of the endocrine side effects of ketoconazole and its excellent penetrability into the CSF of both normal and inflamed meninges.** Fluconazole is employed ***prophylactically,*** with some success, for reducing fungal infections in recipients ***of bone marrow transplants.***

- **Mechanism of action: Like Ketoconazole**
- Fluconazole is effective against all forms of **mucocutaneous candidiasis.**
- Fluconazole is **administered orally or intravenously.** Its **absorption is excellent** and, **unlike that of ketoconazole, *is not dependent on gastric acidity.***
- **Binding to plasma proteins is minimal.**

- The drug **is excreted via the kidney**, ***and doses must be reduced in patients with compromised renal function.***

- **Concentrations** measured in the **urine, tears, and skin are approximately 10 times the plasma concentration, only 10% of elimination is due to metabolism**, the remainder being **excreted** in **urine** and **sweat.**

- Fluconazole **has no endocrinologic effects**, because it ***does not inhibit the CYP450 system*** responsible for the synthesis of androgens.
- Fluconazole **is secreted in human milk** at **concentrations similar to plasma.**
- Fluconazole therapy **has been associated with QT interval prolongation.**

- **Side effects: Nausea, vomiting, and rashes. Hepatitis is rare.**
- **Fluconazole is teratogenic, as are other azoles, and should not be used in pregnancy (C).**

- **A dosage of 500–600 mg/day** may be used **for systemic or severe infections**, and, in **urgent infections** such as meningitis caused by yeast, **800 mg/day have been used. Pediatric doses are measured at 6 –12 mg/kg/day.**

- **Azole = Triazole = Voriconazole**
- It is available for **IV** administration and **orally** administration and is approximately **0.95 bioavailable.**
- **Voriconazole is approved for the *treatment of invasive aspergillosis* and seems to have replaced amphotericin B as the treatment of choice for this indication.**

- **Voriconazole penetrates tissues well, including the CNS. *Elimination* is primarily by *metabolism* through the CYP450 2C19, 2C9, and 3A4 enzymes.**
- **One unique problem is a transient visual disturbance that occurs within 30 minutes of dosing.**
- **DOSAGE FORMS**
- **Injection, powder for reconstitution: 200 mg,**
- **Powder for oral suspension: 200 mg/5ml,**
- **Tablet: 50 mg, 200 mg.**

- **ADVERSE REACTIONS**
- **Hallucinations**, Fever , chills , headache
- **Hypokalemia**
- Nausea , vomiting , abdominal pain .

- **CONTRAINDICATIONS** :
- Hypersensitivity to voriconazole or any component of the formulation.
- coadministration with barbiturates (long acting), carbamazepine, ergot alkaloids, rifampin, rifabutin.

- **DRUG INTERACTIONS :**
- **Calcium channel blockers: Serum levels** may be **increased**, including felodipine, nifedipine, and verapamil).
- **Omeprazole:** Voriconazole may **increase** omeprazole serum levels. In patients taking **≥ 40 mg** of omeprazole per day, **dose** of omeprazole **should be reduced by half.**
- **Warfarin:** Anticoagulant effects may be **increased**; monitor INR.

- **Echinocandins :**
- **Caspofungin, micafungin, and anidulafungin.**
- Echinocandins interfere with the synthesis of the **fungal cell wall** by **inhibiting the synthesis of β(1,3)-D-glucan**, leading to lysis and cell death. This **drug's** spectrum is **limited to Aspergillus and Candida species.**
- ***Caspofungin is not active by the oral route.***
- **DOSAGE FORMS**
- **Injection, powder for reconstitution: 50 - 70 mg.**

- ***Elimination*** **is approximately equal between the *urinary and fecal routes.***

- **Adverse effects** include **fever, rash, nausea, and phlebitis**.
- **Caspofungin *should not be* coadministered with cyclosporine.**

- **Caspofungin** is a **second-line antifungal** for those who **have failed or cannot tolerate amphotericin B or an azole**.

- **Allylamines-thiocarbamates**
- **(terbinafine hydrochloride** and **naftifine hydrochloride) are reversible noncompetitive inhibitors of the fungal enzyme sequalene monooxygenase (sequalene 2,3-epoxidase),** which **converts squalene to lanosterol.**
- This plus the accumulation of toxic amounts of squalene result in the death of the fungal cell.

- **Allylamines - thiocarbamates**

- **Terbinafine**
- Terbinafine is the **drug of choice for treating dermatophytosis and, especially, onychomycosis (fungal infections of nails).** It is better tolerated, **requires shorter duration of therapy**, **and is more effective than either itraconazole or griseofulvin.**

- **Antifungal spectrum**: Antifungal activity is limited to **dermatophytes and Candida albicans**. **Therapy is prolonged usually about 3 months.**
- **Pharmacokinetics** : **Terbinafine is orally active**, although its **bioavailability is only 0.4 due to first-pass metabolism.**
- **It is greater than 99 percent bound to plasma proteins. It is deposited in the skin, nails, and fat.**

- **Terbinafine accumulates in breast milk** and, therefore, **should not be given to nursing mothers.**
- **A prolonged terminal half-life of 200 to 400 hours may reflect the slow release from these tissues.**
- **Terbinafine** is ***extensively metabolized*** prior to urinary excretion.

- **Side effects**: are gastrointestinal disturbances ***(diarrhea, dyspepsia, and nausea), headache, and rash***. **Taste and visual disturbances have been reported *as well as transient elevations in serum liver enzyme levels***.
- Although terbinafine is extensively metabolized, there **does not seem** to be a significant **risk** of **reduced clearance of other drugs**.
- **Rifampin decreases blood levels of terbinafine, whereas cimetidine increases blood levels of terbinafine.**

- **Dosage reductions** are **required with *renal or hepatic* insufficiency**.

- **Oral terbinafine is generally well tolerated but *occasionally causes gastric distress and liver enzyme elevation.***

- **ALLYLAMINES**
- **Naftifine hydrochloride (*Naftin*) is available for *topical* use *only* in the treatment of cutaneous dermatophyte and *Candida* infections.**

- Sources
  http://en.wikipedia.org/wiki/Antifungal
- http://www.lamisil.com/
- http://www.tinactin.com/
- http://en.wikipedia.org/wiki/Griseofulvin
- http://www.journals.uchicago.edu/CID/journal/issues/v30n4/990666/990666.text.html?erFrom=-48603785169359057 51Guest
- http://en.wikipedia.org/wiki/Nystatin
- http://inventors.about.com/library/inventors/blnystatin.htm

- **WWW sites**
- Please note that this list is by no means exhaustive!
- **Fungal infections, general**
- http://www.clinical-mycology.com
- http://fungus.utmb.edu/mycology
- http://www.doctorfungus.org/
- http://www.medicalmycology.org/
- http://www.medsche.wisc.edu/medmicro/myco/mycology.htm
- http://www.fungalforum.com
- **Specific infections**
- http://www.aspergillus.man.ac.uk
- http://www.genolist.pasteur.fr/CandidaDB
- http://www.panix.com/~candida/
- http://alces.med.umn.edu/Candida.html

Parenteral Nutrition Formula Calculations and Monitoring Protocols

1 gr Dextrose → 3.4 kcal

1 gr Lipid → 10 kcal

1 gr A.A → 4 Kcal

Evaluation of a PN Order

PN 15% dextrose, 4.5% a.a. 3% lipid @ 100 cc/hour for 24 hours.

- **Total volume = 2400 ml**
- **Dextrose:** 15g/100 ml * 2400 ml = 360 g
- 360 g x 3.4 kcal/gram = **1224 kcals**
- **Lipids** 3 g/100 ml x 2400 ml = 72 g lipids
- 72 x 10 kcals/gram = **720 kcals**

Evaluation of a PN Order

- **Amino acids:** 4.5 grams/100 ml * 2400 ml = 108 grams protein
- 108 x 4 = **432 kcals**

- **1224 + 720 + 432 = 2376 total kcals**
- **Lipid is 30% of total calories**
- **Dextrose is 51.5% of total calories**
- **Protein is 18% of total calories**

Example Calculation 2-in-1

Nutrient Needs / day:

Kcals: 1800. Protein: 88 g. Fluid: 2000 cc/ day

1800 kcal x 30% = 540 kcal from Lipid (10%):

- 540 kcal/1.1 (kcal/cc) = **491 cc/24 hr =**

20 cc/hr 10% lipid (round to 480 ml)

- Remaining fluid needs: 2000cc - 480cc = **1520 cc**

Protein Calculations

Remaining fluid needs: 2000cc - 480cc = **1520cc**

Protein: 88 g / 1520 cc x 100 = 5.8% amino acid solution

88 g. x 4 kcal/gm =352 kcals from protein

- Remaining kcal needs: **1800 – (528 + 352)** = **920** kcal

Dextrose Concentration

- Remaining kcal needs: 1800 – (528 + 352) = **920 kcal**
- 920 kcal/3.4 kcal/g = 270 g dextrose
- 270 g / 1520 cc x 100 = 17.7% dextrose solution
- Rate of Amino Acid / Dextrose:
- 1520 cc / 24hr = 63 cc/hr

TPN recommendation: Suggest two-in-one PN 17.7% dextrose, 5.8% a.a. @ 63 cc/hr with 10% lipids piggyback @ 20 cc/hr

Re-check calculations

TPN recommendation: Suggest two-in-one PN **17.7% dextrose, 5.8% a.a. @ 63 cc/hr** with **10% lipids piggyback @ 20 cc/hr**

63 cc/hr x 24 = **1512 ml**

1512 * (.177) = 268 g **D** X 3.4 kcals= **911** kcals

1512 * (0.058) = 88 g **a.a**. x 4 kcals = **352**

20 cc/hr **lipids*24** = 480*1.1 kcals/cc = **528**

1791

Sample Calculation 3-in-1

- **Nutrient Needs / day:**
  - **Kcals: 1800, Protein: 88 g Fluid: 2000 cc**
- **Lipid** : 1800 kcal x 30% = **540 kcal**
  - 540 kcal / 10 kcal per gram = **54 g**
  - 54 g / 2000 cc x 100 = **2.7% lipid**
- **Protein: 88 g** / 2000 cc x 100 = **4.4% amino acids**
- 88 g x 4 = **352 kcals from protein**

Sample Calculation 3-in-1(cont)

Dextrose: 908 kcal (1800 – 540 **-** 352)

- 908/3.4 kcal/g = **267 g dextrose**
- **267** g / 2000 cc x 100 = **13.4% dextrose solution**
- **Rate of infusion:** Amino Acid / Dextrose/Lipid: 2000 cc / 24hr **= 83 cc/hr.**
- **TPN prescription: Suggest TNA 13.4% dextrose, 4.4% amino acids, 2.7% lipids at 83 cc/hour provides 88 g. protein, 1800 kcals, 2000 ml fluid**

Acute Inpatient PN Monitoring

Parameter	Daily	Frequency 3x/week	Weekly
Glucose	Initially	√	
Electrolytes	Initially	√	
Phos, Mg, BUN, Cr, Ca		Initially	√
TG			√
Temperature	√		
Bili, LFTs		Initially	√

Inpatient Monitoring PN

Parameter	Frequency Daily	Weekly	PRN
Body Weight	Initially	√	
Nitrogen Balance		Initially	√
HGB, HCT		√	
Catheter Site	√		
Lymphocyte Count	Initially		√
Clinical Status			√

PRN : Pro – Re – Nata = when necessary

Monitoring: Nutrition

Serum Hepatic Proteins

Parameter	Time
Albumin	19 days
Transferrin	9 days
Prealbumin	2 – 3 days
Retinol Binding Protein	~12 hours

Osmolarity Quick Calculation

To calculate solution osmolarity:

- **(A).** multiply grams of **dextrose per liter by 5**
- **(B).** multiply grams of **protein per liter by 10**
- **(C).** add A & B
- add 300 to 400 to the answer from “C". (Vitamins and minerals contribute about 300 to 400 mOsm/L.)

Is the solution compoundable?

- TPN is **compounded using 10% or 15% amino acids, 70% dextrose, and 20% lipids**
- The TPN prescription must be compoundable using standard base solutions
- This becomes an issue if the patient is on a fluid restriction

Is the Solution Compoundable?

What is the minimum volume to compound the PN prescription?

Example: **75 g AA**
350 g dextrose
50 g lipid
2000 ml fluid restriction

AA: **10 g** = 75 g = **750 ml using 10% AA**
100 ml X ml

OR divide 75 grams by the % base solution, 75 g/ .10

Is the solution compoundable?

Dextrose: $\frac{70\ g}{100\ ml} = \frac{350\ g}{X\ ml}$ x = **500 ml**

Lipid: $\frac{20\ g}{100\ ml} = \frac{50g}{x\ ml}$ X = **250 ml**

Total volume = 750 ml AA + 500 ml D + 250 ml lipid + 100 ml (for electrolytes/trace) = 1600 ml (minimum volume to compound solution)

Tip: Substrates should easily fit in 1 kcal/ml solutions

Is this solution compoundable?

PN prescription:

AA 125 g

D 350 g

Lipid 50 g

Fluid restriction 1800 ml/day

Is this solution compoundable?

AA: **10 g** / 100 ml = 125 g / X ml = **1250 ml** (125 /. 10)

Dextrose: **70 g** / 100 ml = 350 g / X ml x = **500 ml** (350/.70)

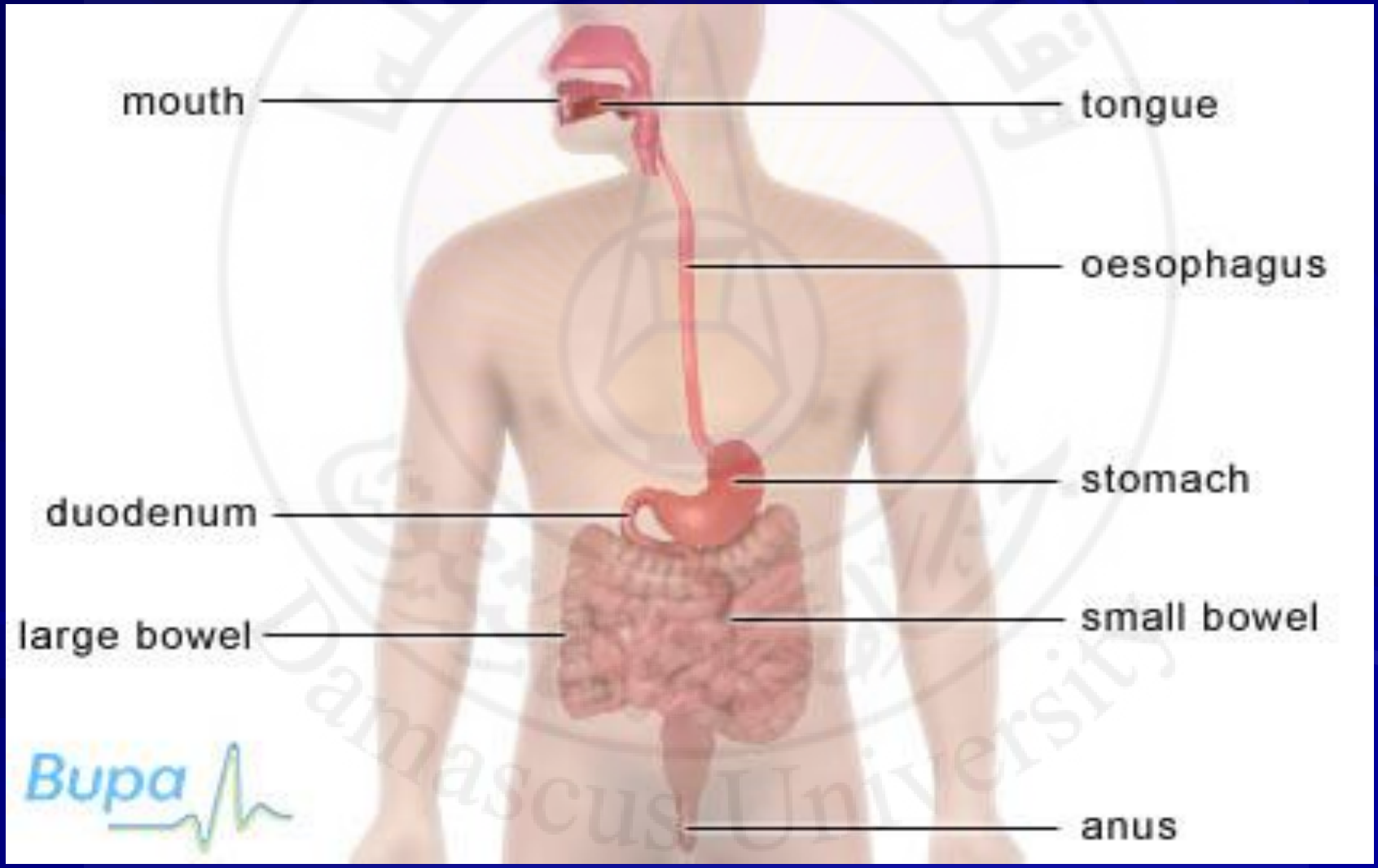
Lipid: **20 g** / 100 ml = 50g / x ml X = **250 ml** (50/.20)

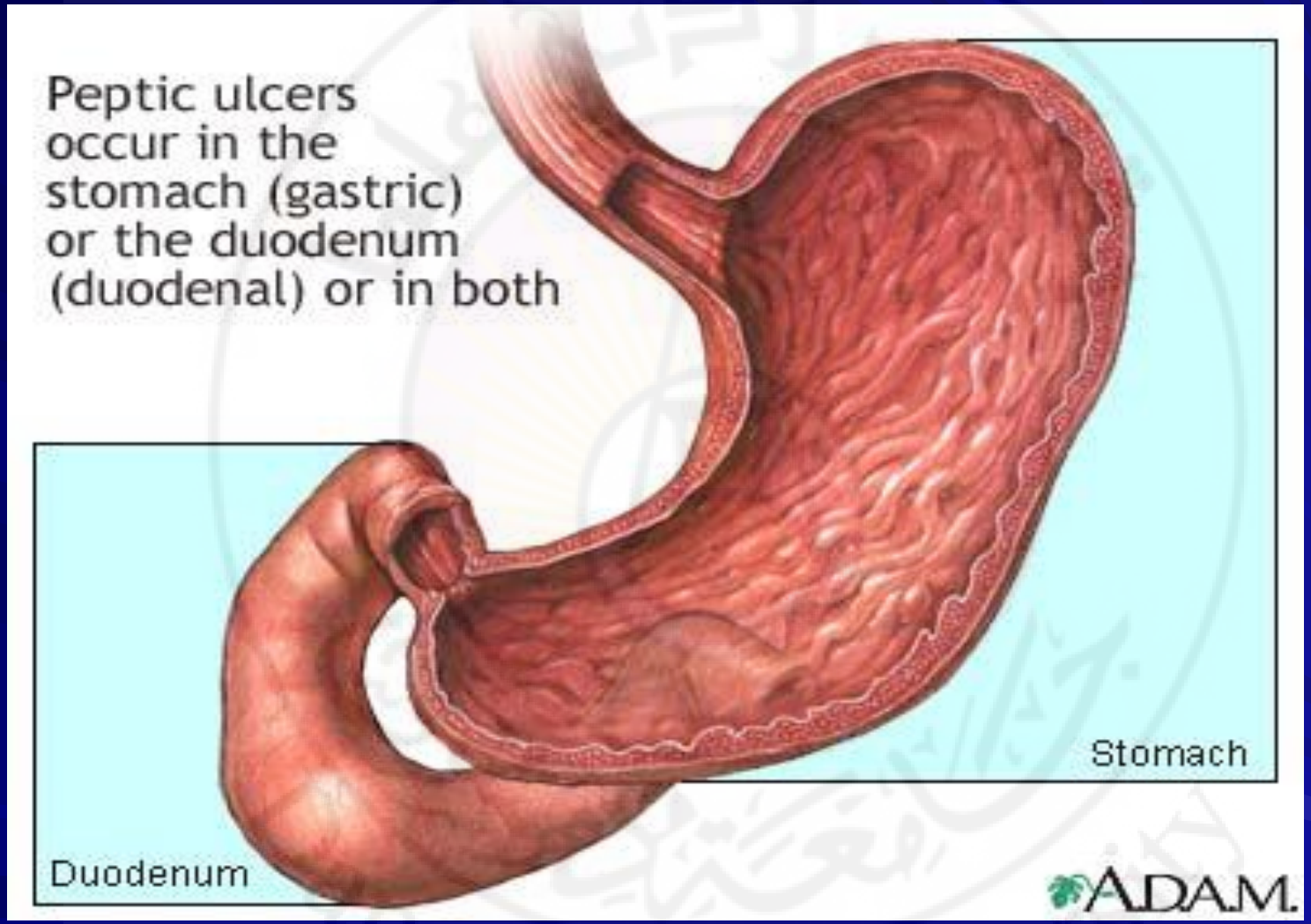
Total volume = 1250 ml AA + 500 ml D + 250 ml lipid + 100 ml (for electrolytes/trace) = **2100 ml** (minimum volume to compound solution)

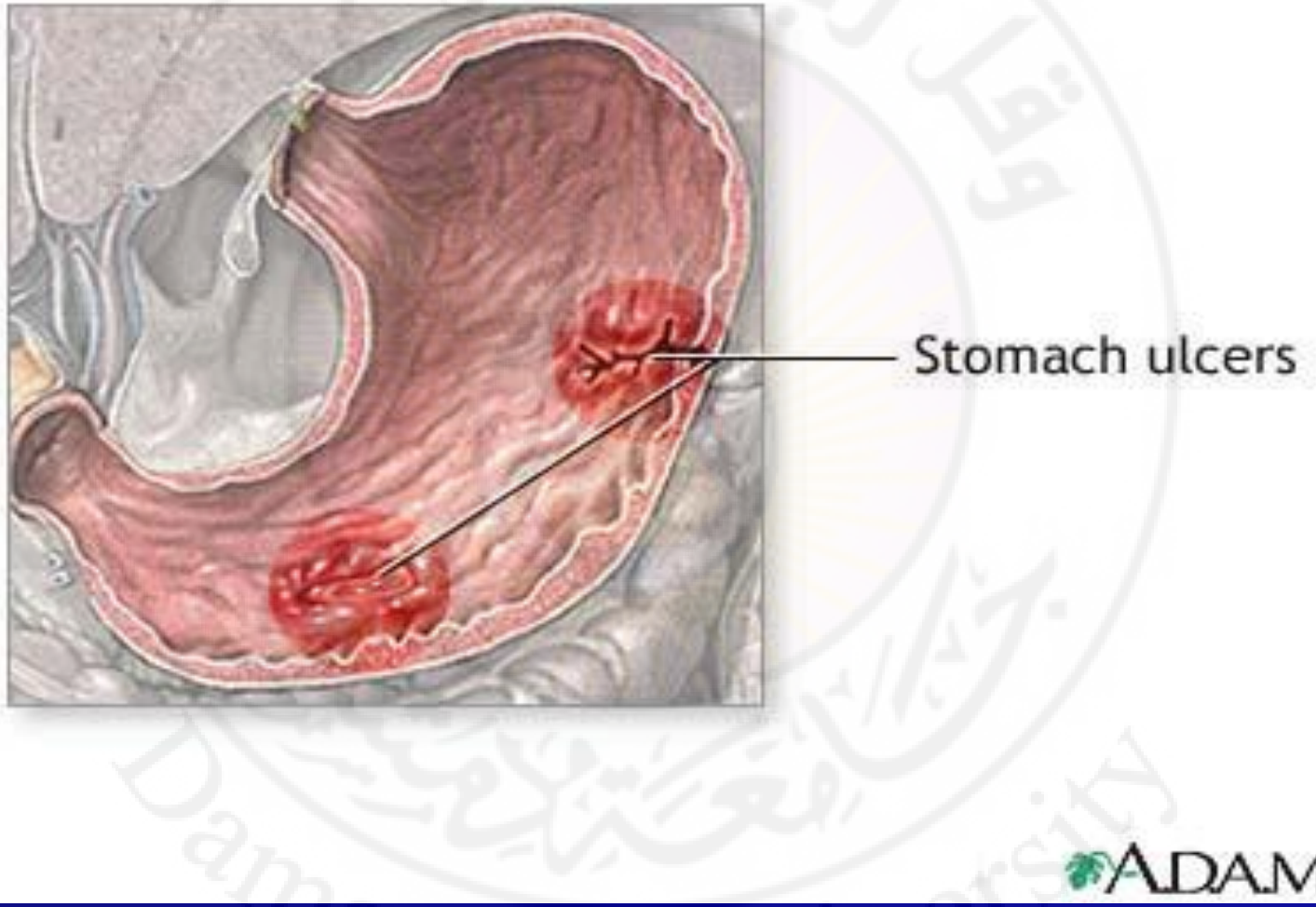
Verdict: not compoundable in 1800 ml.

Action: reduce dextrose content *or* use 15% AA base solution if available (could deliver protein in 833 ml of 15%)

PEPTIC ULCER, PUD




Peptic ulcers occur in the stomach (gastric) or the duodenum (duodenal) or in both
Stomach
Duodenum
A.D.A.M.


Stomach ulcers
A.D.A.M.

Definistion

- A peptic ulcer is an open sore or raw area in the lining of the stomach (gastric) or the upper part of the small intestine (duodenal).
- **An ulcer is a crater-like lesion on the skin or mucous membrane caused by an: inflammatory, infectious, or malignant condition .**

- Ulcers of the small intestine are known as ***duodenal ulcers.*** Duodenal ulcers affect about ***1 in 10 people*** at some point in their lives, usually between the ***ages*** of ***45 and 65.***
- **Stomach ulcers are less common**, and usually affect people aged ***over 65.***

- ***Causes***
- **The following are the most important causes of peptic ulcers:**
- **The most common cause is infection of the stomach with:**
- ***1).*** **bacteria called *Helicobacter pylori* or *H. pylori*. This infection is quite common; about half of the world's population is infected. These bacteria cause the stomach to make too much acid, which damages the lining of the stomach or duodenum and can cause the ulcer.**

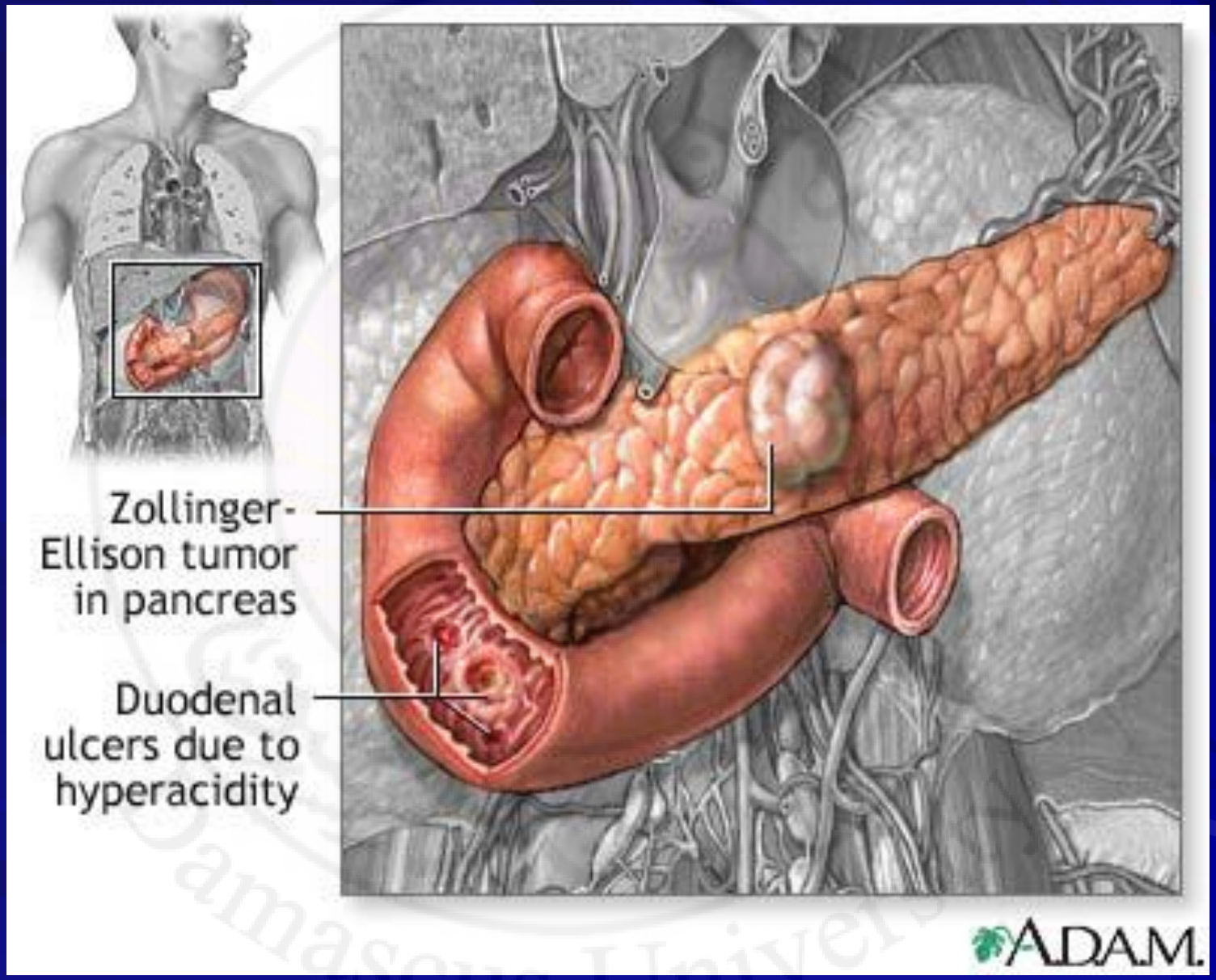
- ***2).*** **Non-steroidal anti-inflammatory drugs (NSAIDs),** can cause peptic ulcers. Examples : **aspirin, ibuprofen, naproxen and diclofenac.** However most people can take these safely.

- ***3).*** **Smoking and drinking excessive alcohol.**

- ***4)***. **Stress** is widely thought to cause ulcers, but this **has not been proven**. It could be that **people under lots of stress are more likely to smoke and drink too much.**

- ***5).*** **Zollinger-Ellison syndrome** egral A . tnuoma**of excess acid is produced in** response to the overproduction of the **hormone gastrin** si nrut ni hcihw ،**caused by** ***tumors*** eht no ***pancreas or duodenum*** . eb tsum ،tnangilam yllausu era sromut esehT ot desserppus noitcudorp dica dna devomer .sreclu eht fo ecnerrucer eht eveiler

- ***6).*** Coffee, tea, cola beverages, beer, and spices **may cause dyspepsia** ***but do not increase PUD risk?.***


Zollinger-
Ellison tumor
in pancreas
Duodenal
ulcers due to
hyperacidity
A.D.A.M.

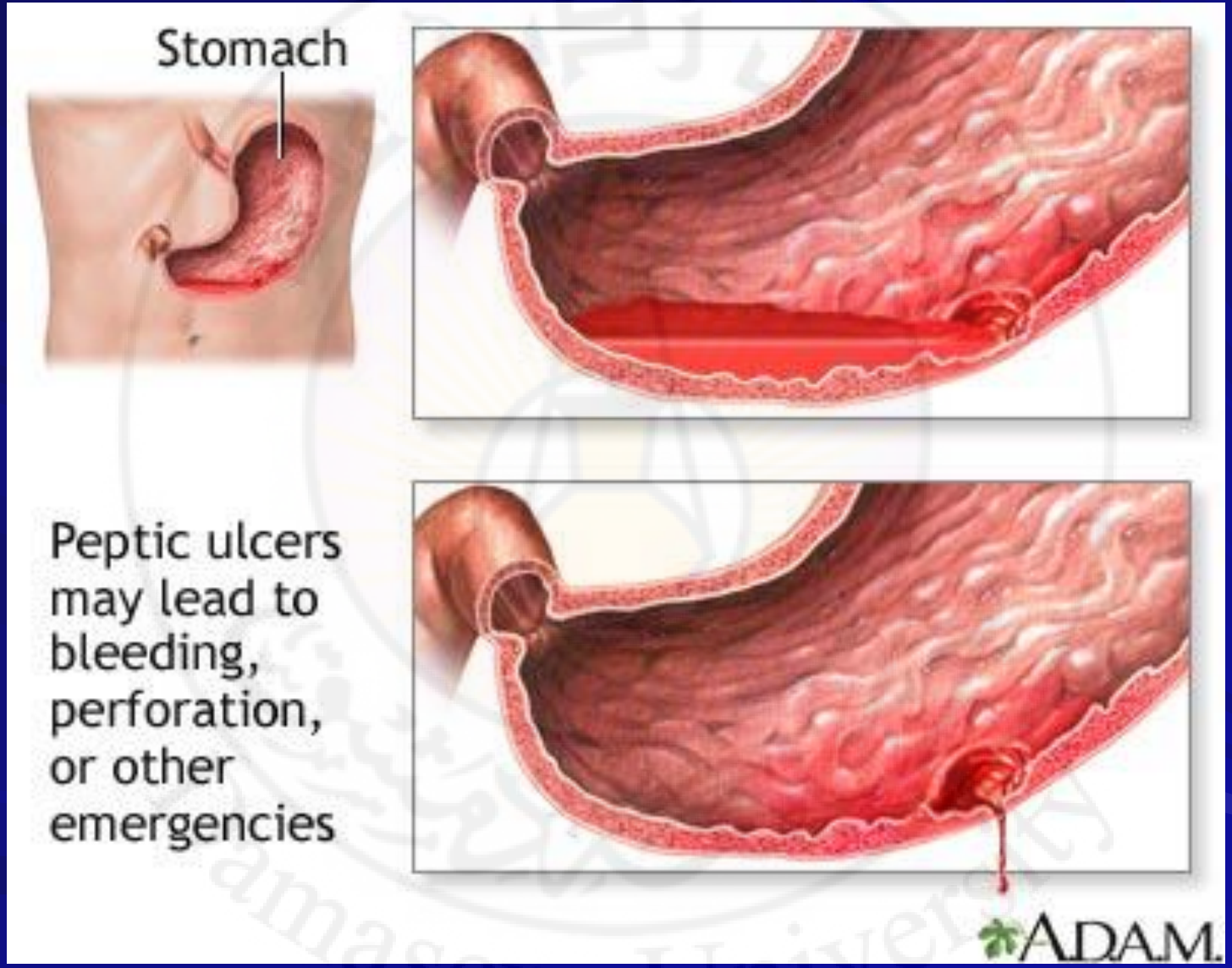
- ***Symptoms***
- **Some people** with a peptic ulcer **have no symptoms.** However, many people have **upper abdominal pain** usually just below the breastbone (sternum). **Feel a pain in a back**. The pain usually comes on an hour or two after eating and can be relieved by more food or antacid medicine. It may also **wake you at night especially between 12 am and 3 am.**

- ***Other symptoms may include*:**
- belching : تَجَشُّؤ
- heartburn
- general discomfort in the abdomen
- bloating or fullness after eating
- feeling sick
- vomiting
- difficulty swallowing
- lost weight without trying to do
- a reduced appetite
- seen blood in a vomit or bowel movements

Complications

- **Possible** complications include the following **:**

- **Bleeding**
- Occasionally ulcers can cause the lining of the stomach or duodenum to bleed.
- A bleeding ulcer will give symptoms that include**:**
- vomit containing dark brown bits of clotted blood (with an appearance like ground coffee)


Stomach
Peptic ulcers may lead to bleeding, perforation, or other emergencies
A.D.A.M.

- blood in the faeces (usually dark red) black, tarry faeces.

- **Anaemia : Chronic iron deficiency**
- If the bleeding from the ulcer is slow, you might not get blood in your vomit or faeces. However, you may develop anemia.

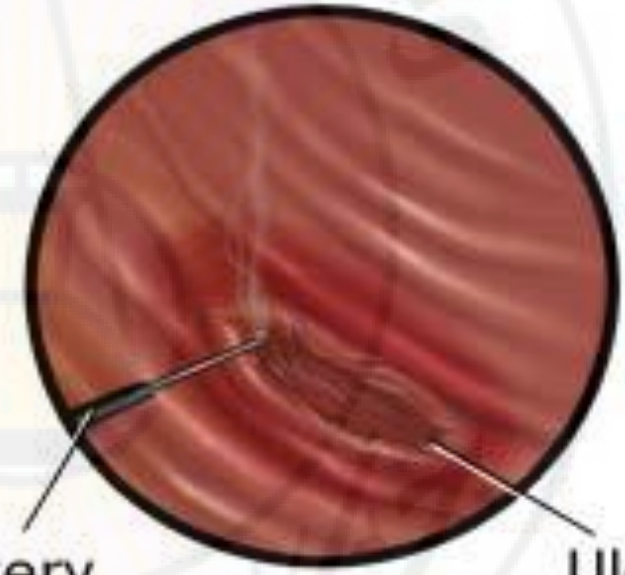
- **Perforation**
- Rarely, the ulcer may erode very deeply into the wall of the stomach or duodenum, leaving a hole into the abdomen. **This causes severe pain and needs emergency surgery.**

- **Diagnosis**
- The tests to diagnose, are.
- ***H. pylori tests:***
  - Testing for *H. pylori* : ***breath***
  - (**breath**) *urea* $\longrightarrow$ $Co_2 + NH_3$ *(90%)*
  - (**stool**) test. H pylori **antigen** (90%)
  - (**blood)** : anti H pylori **IgG antibodies**
  - (# Active or previous infection).

- **If an anti-ulcer proton pump inhibitor (PPI) is used, the breath and faeces test won't be accurate until two weeks after stopping the medicine.**

- ***Endoscopy***
- The endoscopy is the only way to be certain whether you have a peptic ulcer.

View of a duodenal ulcer through the endoscope



A.D.A.M.

- A flexible, tube-like instrument called a **gastroscope** is passed through the mouth and into the stomach, usually under sedation in hospital. The procedure usually **lasts a few minutes.**

- **With the instrument :**
- looking the lining of the stomach, and
- can take a sample of stomach lining or a biopsy for laboratory, or
- **directly tested for *H. pylori*.**

- **Treatment: Drugs**
- **Three major landmarks for peptic ulcer disease**
- **1) The first : *H2 Receptor Antagonists*** (H2RA) of
- which the first was cimitidine.
- Ranitidine, Famotidine , Nizatidine **Lavoltidine**
- **Structural : analogues to histamine**
- **Blockage : histamine receptor**
- ⟶ decreasing Hcl secretion
- **Preventing conversion of pepsinogene to pepsin (acid PH medium).**

- **Tmax = 1 – 3 hr**
- ***Elimination = Kidneys***
- **Dose adjustment (renal failures)**
- Evening Dose Administration (PH low)
- **ADR** : Diarrhea, Headache, confusion
- **Drug – interaction :**
- Cimitidine : **Reduction Cl int (oxidation) of :**
  - Theophylline = Cl reduced (40%), Toxicity
  - Phenytoin + bezodiazepines = Met reduced
  - **itraconazole + Ketoconazole = Abs reduced**
  - ***Css aver Warfarin increase***
- ***Proffered (over PPI) in pregnancy***

- ***Bismuth Chelate*** (Safe form of bismuth)
- Cytoprotective properties
- Toxic to H pylori (ranitidine + bismuth chelate +
- 2 antibiotics) leads to 90% efficacy H pylori.

- **ADR :**
- **Accumulation in impairment renal**, nausea,
- vomiting, ***dark faces, black end langue.***

- ***Sucralfate : Al sucrose octasulphate***
- Mechanism : Stimulation of bicarbonate
- Stimulation of mucus secretion
- Stimulation of prostanoid, eg :
- (prostaglandin, thromboxane, prostacyclins)

- PH < 4 : it form sticky viscid gel, adheres to ulcer surface
- Dose = 2 gr twice daily .
- ADR = risk Al toxicity (long terms)
- **Caution in renal impairment**
- **Interactions = reducing absorption some drugs:**
- Antifungal agents, azole, (itraconazole, ketoconazole)
- (ciprofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, sparfloxacin)
- Phosphate supplements (oral). interval = 2 hr

- 2) The second : **proton pump inhibitors (PPI)** of which **omeprazole** was the first.
- Lansoprazole, Pantoprazole, Esomeprazole,
- Rabeprazole, Binzinidazole,
- Pro-drug: converted to drug, which binds to PP
- Site of action : Secretory canaliculus
- Dosage forms : enteric coating
- Half-life : 1 – 2 hr
- Duration of action : 45 - 50 hr
- Dosing intervals : 24 hr

- Effectives : 30 min before a meal
- **(Ideal = 30 – 60 min before first meal)**
- **Elimination : Hepatic (80%) conjugation**
- **ADR** : Diarrhea – headache, abdominal pain,
- change in intestinal PH + Bacterial over growth
- Long term : Respiratory tract infection **(clos diff)**

- **Drug interaction :**
- **Omeprazole inhibit Cyp450 : 2C9 – 2C19**
- ***Lansoprazole : induce Cyp 450 : 1A2***
- **PPI > H2RA : Efficacy**

- **3)** The third was the discovery that **H pylori** is associated with much peptic ulcer disease, and with this came the rationale for **eradication** of the organism. As a result of these innovations, the need for surgery for peptic ulcer has been dramatically reduced.
- **H pylori infection** is associated with about 95% of duodenal ulcers and 80% of gastric ulcers. The remainder are mainly **related** to **NSAIDs**. **Bisphosphonates** and **corticosteroids** may also be implicated.

Contraindications

- Many of the drugs used in the management of peptic ulcer disease carry a warning that **they *should not be used in pregnancy* or whilst *breast feeding*.**
- The exception is **misoprostol**, a **prostaglandin analogue**, ***that should be avoided in pregnancy*** as it may **cause abortion.**
- If H pylori eradication is used, it may be necessary to avoid a certain antibiotic if the patient is allergic. For example, **amoxicillin** may be replaced by either **tetracycline** or **metronidazole.**

- **Indications**
- Symptomatic management of **ulcer dyspepsia** and **non – ulcer dyspepsia**
- **1)**. Healing of gastric or duodenal ulcers
- **2)**. Eradication of Helicobacter pylori
- **3)**. Healing of ulcers related to drugs. This is usually the **NSAIDs** and in some cases it may be desirable to continue the drug and to give something to heal the ulcers.

- **Caution**
- Beware of the possibility of failing to diagnose **gastric malignancy**.
- **PPIs are metabolised mostly in the liver.**
- **In liver disease, do not exceed the following doses:**
  - 20 mg daily for **omeprazole, Pantoprazole, and esomeprazole;**
  - 30 mg daily for **lansoprazol**
  - There are no data on the use of **rabeprazol** in people with severe hepatic impairment so the manufacturer advises caution.(20 mg daily)

- **Omeprazole and esomeprazole may interfere with *warfarin* monitoring.**

- **If metronidazole is used, remember to warn the patient to avoid alcohol.**

- **Initiation of treatment**
- **Management** is not just pharmacological but **should include attention** to **lifestyle**. This may include **:**
- **stopping smoking,**
- **more regular meals,**
- **ceasing excessive alcohol consumption** and
- **possibly stopping drugs that may be contributing to the problem.**

- **Choice of treatment**
- ***Antacids*** are cheap, simple and may be all **that is required for *relief* of occasional *symptoms*.**
- ***H2RAs*** provide a **swift** and effective means of acid suppression and can be used intermittently to achieve control of symptoms.
- ***PPIs*** are more prolonged in action, produce more profound acid suppression.

- ***Misoprostol*** tends to be **used to heal NSAID associated ulcers.**

- Using a **prostaglandin analogue** to heal ulcers antagonism, **tend to cause diarrhoea too** and may be unacceptable. ***Proprietary combinations of NSAID with misoprostol are available.***

- Attempts should be made to eradicate Helicobacter pylori whenever it is found, whether the diagnosis is duodenal ulcer, gastric ulcer, **NSAID induced ulcer or even non-ulcer dyspepsia.**

- **Symptomatic relief**
- *Simple* ***antacids*** will usually give symptomatic *relief of fairly short duration*. However, such relief is very non-specific and **should not be taken as indicative of peptic ulcer disease.**
- Heartburn may also occur in this condition although it is more typical of **gastro-oesophageal reflux disease**. **An antacid alginate mixture is usually preferred for reflux.**

- More profound and prolonged acid suppression may be achieved with a **H2RA or, better still, a PPI.**

- **Clinical Knowledge Summaries**
- recommend that if an **ulcer is proven** but **H pylori testing is negative**, then ***acid suppression*** **at full dose should be offered for 1 or 2 months.** **A lower maintainance dose** may be **continued after.** The ***full course*** should be taken as there is little correlation between the relief of symptoms and the healing of ulcers **and if medication is stopped too soon the ulcer will relapse.**

Helicobacter pylori eradication

The following is based on the recommendations of NICE:

omeprazole 20mg •

- amoxicillin 1000mg
- Clarithromycin 500mg, **all** twice daily for 21days.
-

An alternative regimen with a similar eradication rate of around 90% is:

- omeprazole 20mg
- clarithromycin 250mg
- metronidazole 400mg, again **all** twice daily for 21days.

- It is common practice to **use 4 drugs** for a repeated attempt. The antibiotics can be changed and chelated bismuth may be used. ***A typical quadruple therapy would be:***
- ***PPI twice** a day*
- ***Bismuth chelate** 120 mg **4 times** a day*
- ***metronidazole** 400 mg **3 times** a day*
- ***Oxytetracycline** 500 mg **4 times** a day, all for 21days.*
- Reinforce the importance of compliance as it is not easy to take so many tablets so many times a day, **even for just a week**.

- **Ulcers associated with NSAIDs**
- **If a drug is thought to be the cause of peptic ulceration, it is sensible to stop the drug or change it to another with a lower risk. There may be times when it is desirable to continue that drug. An old person may need treatment for arthritis to maintain mobility or aspirin may be required in cardiovascular disease. It is often possible to heal the ulcer without stopping the offending drug and a maintenance dose is continued to prevent relapse.**

- **Clinical Knowledge Summaries** recommend that **omeprazole 20 mg daily** is ***preferable*** to **ranitidine 150 mg twice daily** as the respective rates of healing are **80%** and **63%.**

- H2RAs are slow to heal the ulcers if the offending drug is not stopped and so, under these conditions, a ***PPI is preferred.***

- **H pylori eradication is no more effective than omeprazole alone** to heal ulcers, ***but*** **if the *infection is present*, then *eradication will reduce the rate of relapse.***

- **Monitoring**
- Patients should be reviewed at the end of a course of treatment, especially H pylori eradication, to confirm a satisfactory outcome.

- ***Repeat endoscopy may be required for*** **:**
- **Failure to eradicate symptoms** in a duodenal ulcer.
- **Failure to have eradicated H pylori.**

- Follow up of a gastric ulcer requires repeat endoscopy to confirm healing at 6 to 8 weeks along with confirmation of eradication of H pylori.

- **If a gastric ulcer persists, referral to secondary care is required.**

- If it is **healed** but **symptoms persist**, a **course of acid suppression for a limited duration may be in order**, **but if symptoms persist, referral is necessary.**