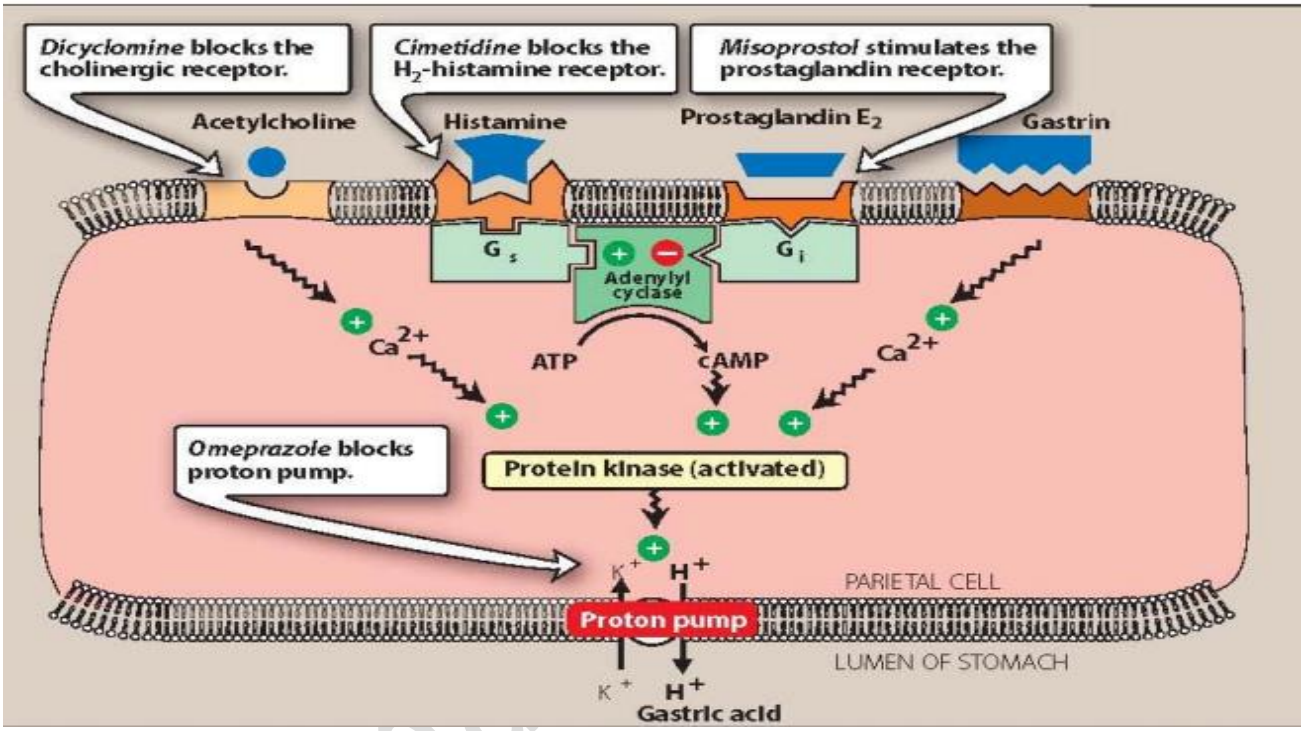
Done by Dr Ahmad Almohtasbe

GI pharma lec 3

GERD and peptic ulcer disease part 2

Summary done by: Dr Ahmad Almohtaseb

Mechanism of Hcl secretion



Peptic ulcer treatment

Eradicate underlying cause of **acid/defenses imbalance:-**

1.H.pylori eradication therapy→higher healing rates!!

2. Remove NSAID(if possible)

Restore **acid**/**defenses** balance

Mucosal protectives(cytoprotectives):-

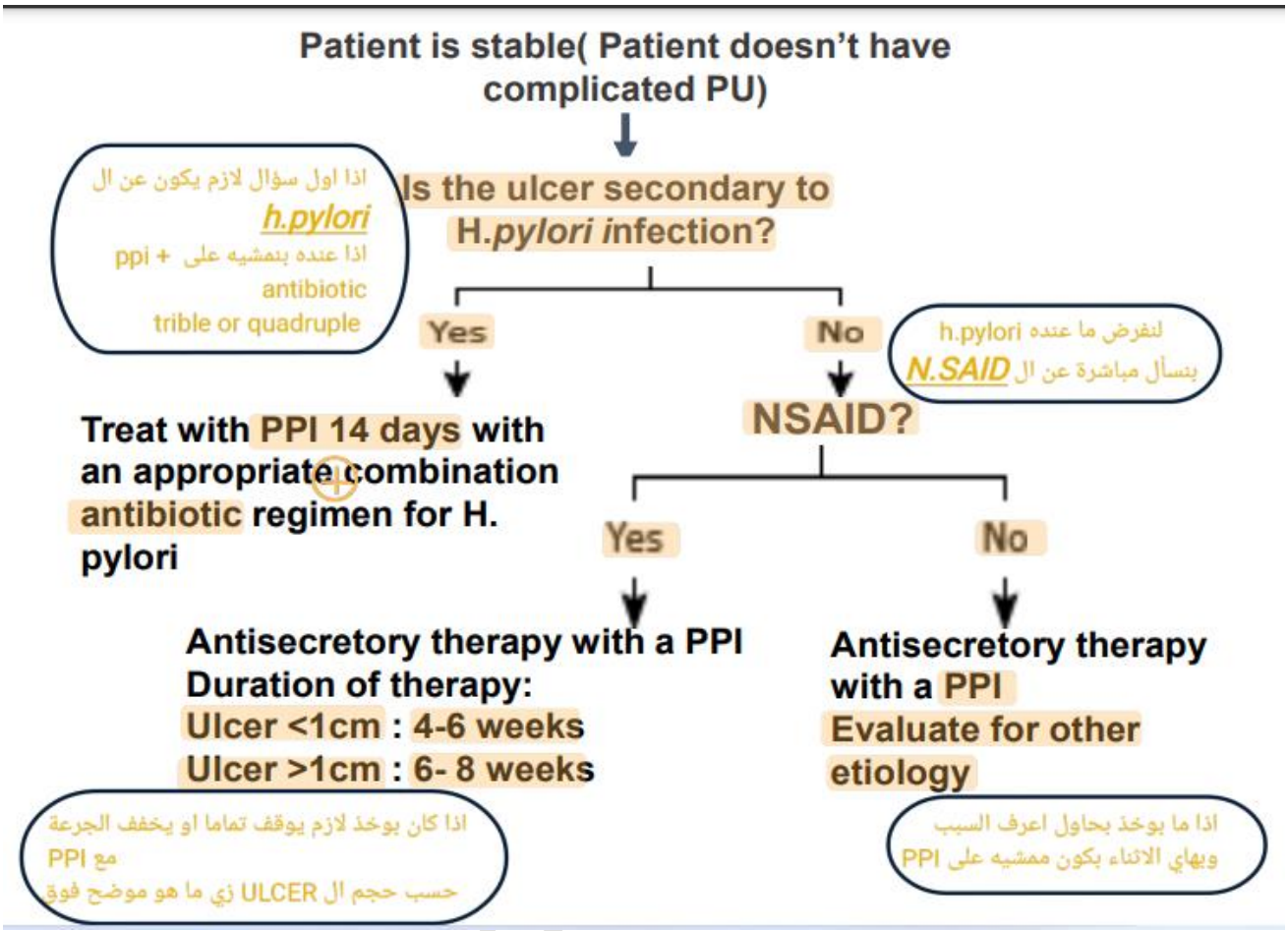
1- Sucralfate 2- Bismuth subsalicylate

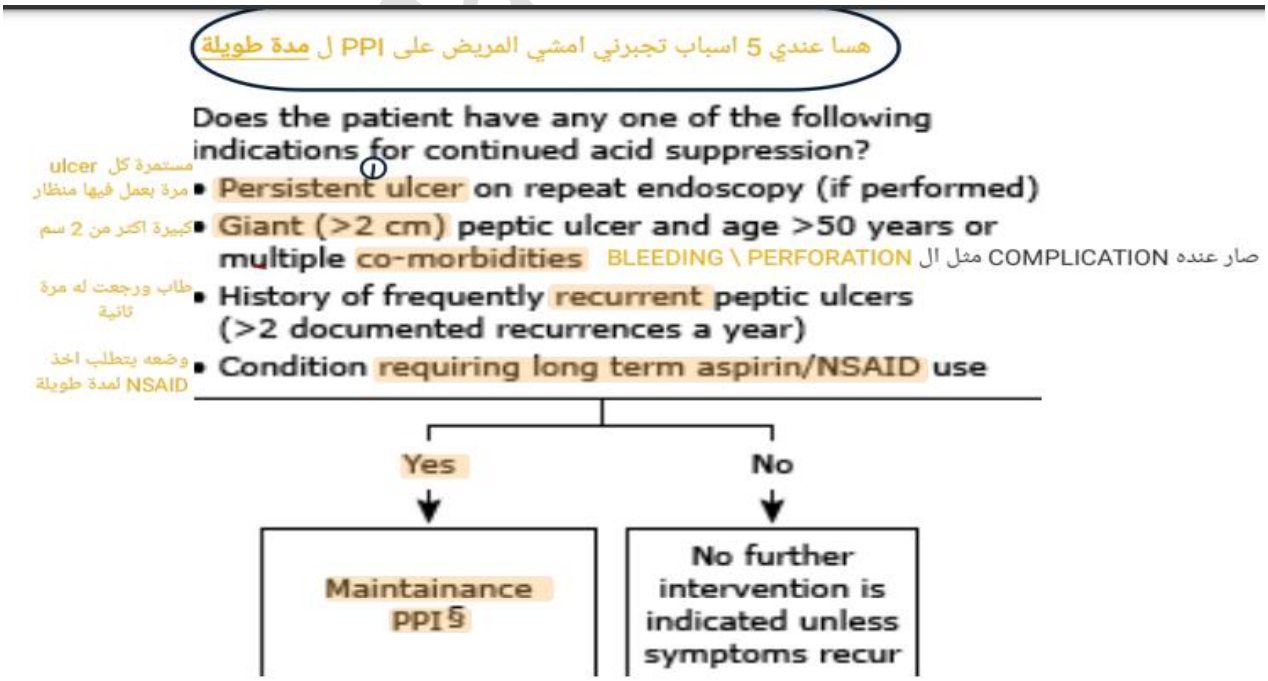
Decrease acidity

Antacids: symptomatic therapy Calcium carbonate, aluminum hydroxide, magnesium hydroxide.

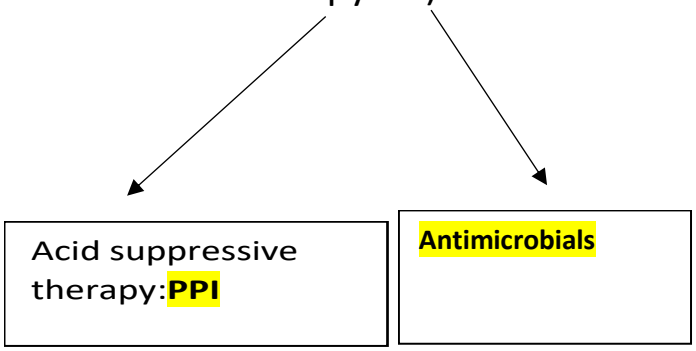
Acid suppressive therapy:-

1- H2 antagonists 2**- Proton pump inhibitors (PPIs)→the strongest!!.** 3- PG analogues (e.g. misoprostol). 4. Antimuscarinic agent: Dicyclomine


Patient is stable(Patient doesn't have complicated PU)
Is the ulcer secondary to H.pylori infection?
اذا اول سؤال لازم يكون عن ال h.pylori
اذا عنده بنمشيه على ppi + antibiotic trible or quadruple
Yes
No
لنفرض ما عنده h.pylori بنسأل مباشرة عن ال N.SAID
NSAID?
Yes
No
Treat with PPI 14 days with an appropriate combination antibiotic regimen for H. pylori
Antisecretory therapy with a PPI
Duration of therapy:
Ulcer <1cm : 4-6 weeks
Ulcer >1cm : 6- 8 weeks
Antisecretory therapy with a PPI
Evaluate for other etiology
اذا كان بوخذ لازم يوقف تماما او يخفف الجرعة مع PPI
حسب حجم ال ULCER زي ما هو موضح فوق
اذا ما بوخذ بحاول اعرف السبب
وبهاي الاثناء بكون ممشيه على PPI


هسا عندي 5 اسباب تجبرني امشي المريض على PPI ل مدة طويلة
Does the patient have any one of the following indications for continued acid suppression?
ulcer مستمرة كل مرة بعمل فيها منظار
• Persistent ulcer on repeat endoscopy (if performed)
كبيرة اكتر من 2 سم
• Giant (>2 cm) peptic ulcer and age >50 years or multiple co-morbidities
صار عنده COMPLICATION مثل ال BLEEDING \ PERFORATION
طاب ورجعت له مرة ثانية
• History of frequently recurrent peptic ulcers (>2 documented recurrences a year)
وضعه يتطلب اخذ NSAID لمدة طويلة
• Condition requiring long term aspirin/NSAID use
Yes
No
Maintainance PPI §
No further intervention is indicated unless symptoms recur

Eradication of Helicobacter pylori (H. pylori)



Antimicrobials:-

1. **Clarithromycin(macrolide): most potent. Related to erythromycin but is more acid stable, better absorbed and more effective against H pylori.**

2. **Amoxicillin:**

3. Tetracyclines

4. Levofloxacin

5. Metronidazole: High resistance rate.

6. Nitroimidazole: to avoid metronidazole resistance.

7. Tinidazole.

Aim of antimicrobial combination strategies :

- Enhance H pylori cure.
- **Shorten duration of treatment (1- 4 weeks). In one week therapy high doses of 3- 4 drugs are used.**
- Decrease treatment failure and resistance
- Decrease recurrence rate.

Eradication of Helicobacter pylori (H. pylori)

Category	Triple Therapy	Quadruple Therapy
Acid suppression	PPI	PPI
Antibiotic 1	Clarithromycin	Tetracycline
Antibiotic 2	Amoxicillin OR Metronidazole (if penicillin allergy)	Metronidazole
Additional agent	—	Bismuth subsalicylate 525 mg QID for mucosal protection
Duration	10–14 days	10–14 days

زي ما هو واضح عالحالتين لازم يمشوا على ppi حتى مرات بحب اني امشيهم لمدة اسبوعين ل ٣ بعد انتهاء فترة العلاج

دائما نفضل ان نعطي ال quadrple اذا ما زبط على ال triple

Acid - suppressive therapy : H2- histamine receptors blockers

H2- histamine receptors blockers **work by competitively blocking the binding of histamine.**

Four drugs:

- **Cimitidine: Has the most adverse effects→ limited use**
- **Famotidine: most commonly used**
- **Nizatidine: recent withdrawal/ recallانسحب من السوق by FDA.-->potential contamination with carcinogen N-Nitrosodimethylamine (NDMA)**
- Ranitidine: **recent withdrawal/ recall by FDA→ potential contamination with carcinogen N-Nitrosodimethylamine (NDMA)**
- As these drugs work by **decreasing acid secretions** therefore **may not relive symptoms of heartburn for up to 45 minutes.(compare that with antacids, which provide rapid relief)**

• H2 blockers Mechanism of action:-

inhibit acid secretion by **blocking H2 receptors on the parietal cell (competitive inhibitors)**

• **Well absorbed after oral dosing**. Distribute wildly throughout the body including **across placenta and into breast milk**

• **Peak serum concentrations occur** within **one to three hours.**

• **Absorption is reduced 10 to 20 percent by concomitant antacid administration, but not by food**.

• **Eliminated by a combination of hepatic and renal metabolism**

• **The dose** of all the H2 antagonists is **generally reduced by 50 percent in patients with severe renal failure**

1. **DU: Short term (acute therapy) leads to healing rate of 70% (on 4 weeks therapy, compare with PPI which leads to same cure rate in just 2 weeks) and 90% (on 8 weeks therapy).**

2. **GU: Less effective and healing is delayed than DU by 2-4 weeks.**

Less effective in healing NSAID induce ulcers.

3. **Stress ulcer (ICU patients): IV injection or infusion is preferred.**

4. **GERD**

5. **Before anesthesia** in e.g. cesarean section to **avoid aspiration pneumonia (Mendelson's syndrome**)

H2 blockers can be **given by slow IV injection or infusion in acute and severe cases.**

H2 antagonists **have less efficacy than proton pump inhibitors they are second choice in GERD and severe PU. PPI are first line**

• Disadvantages/adverse effects of H2 antagonists:

1. **Lack of day time reduction and meal –stimulated Hcl secretion**.

2. **Less potency in anti H pylori combination regimens**.

3. **Lower healing rates in GERD.**

4. **Tolerance because of receptor upregulatiopn**

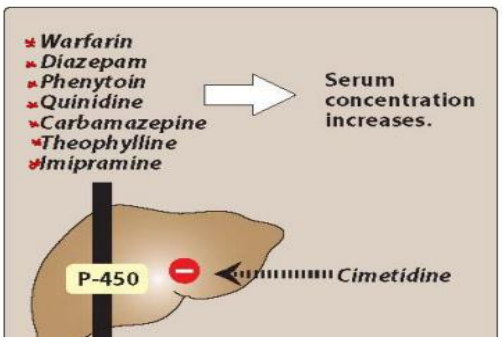
5. Rebound hyperacidity because of receptor upregulation!(if you discontinue H2 antagonists histamine will bind to large number of receptors→ ulcers return back worse!!)

6.**Rapid IV injection** may **cause decrease cardiac output, arrhythmias or heart block**

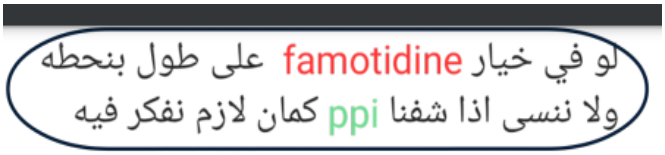
7.Cimetidine:→ CYP-450 Enzyme inhibition!!-->drug interactions!

CYP metabolizes estrogen in body, so cimetidine through CYP inhibition will cause hyperestrogenism with gynecomastia تثدي and galactorrhea إدرار حليب

Cimetidine ما بنعطيهم سوا



NDMA impurities were found to have been introduced during the **manufacturing processes** and as the **result of product degradation** during storage



Acid - suppressive therapy : Proton pump inhibitors

block acid secretion by **irreversibly binding and inhibition of hydrogen-potassium ATPase pump(H+/K+ ATPase)**

PPI use results in **faster control of peptic ulcer disease symptoms and higher ulcer healing rates**

PPIs are also **more effective in preventing and healing NSAID-induced gastroduodenal toxicity than H2 blockers**

So if a question tells you that ulcer is NSAID induced, don't think about H2 blockers, think about PPI

PPIs are a **component of H. pylori antibiotic regimens** and are **used in the treatment of hypersecretory states (eg, gastrinoma)**

Serum t ½ is 1 hour but duration of action is more than 24 hours due to prolonged inhibition of H+ / K+ ATPase. 1st line in PU disease.

Uses of PPI:-

1. DU: for 2-8 weeks. Specially in severe and non responding mild or moderate cases...
2. **GU**: for 4-8 weeks.
3. **Prevention of rebleeding from PU and stress bleeding-->High oral dose or IV infusion increases intragastric pH > 6 and increases coagulation and platelet aggregation.**

So if there is a question about **complicated ulcer that is bleeding**, it is preferrable to give PPI as an infusion or high oral dose than regular oral doses

4. **Zollinger - Ellison syndrome(gastrinoma): Drugs of 1st choice**
5. **GERD:1st line: twice daily PPIs** is used to treat **extraesophageal complication** of reflux disease (asthma , noncardiac chest pain chronic cough and laryngitis

Adverse effects of PPI

Are **both duration and dose – dependent, so short term use will have no symptoms**:

2. **Long term PPIs (as well as H2 antagonists) decrease absorption of vitamin B12, iron and calcium causing their deficiency**→This may cause **hip, wrist & spine fracture**. So, **give calcium supplement.**
3. **Diarrhea, abdominal pain, nausea & vomiting. Headache, dizziness**
4. **Clostridium difficile colitis(pseudomembranous colitis) and pneumonia**

Drug interactions of PPI(very important!):-

• **Omeprazole and esomeprazole inhibits CYP2C19 which prevents the conversion of clopidogrel to its active metabolites →decreasing clopidogrel effectiveness**.

• So, the **concomitant use of Omeprazole and esomeprazole with clopidogrel is not recommended**.

Done by Dr Ahmad Almohtasbe

Prostaglandins

• Mechanism :-

• **Misoprostol : Prostaglandin E analogue**

• **Potent selective cytoprotective**(everything that NSAIDS disturb, prostaglandins correct!!)

1. ↓ Hcl secretion.

2. ↑ mucus secretion and bicarbonate

3. **Stimulates tight junctions in epithelial mucosa in GIT inhibiting back diffusion of H+.**

4. **↑ blood flow to gastric mucosa.(increased healing)**

Uses :-

Prophylaxis for NSAID induce ulcer →reduces serious GI complications in people dependent on NSAIDS like rheumatoid arthritis patients

For healing of GU but not DU.

Prostaglandins have Preventive effect but not totally protective **The most effective is PPI**

Adverse effects:-

1. Severe colicky pain of stomach and intestine.

2. Diarrhea (treated by aspirin).

3. Severe uterine contractions→may cause miscarriage in pregnant ladies(contraindicated) .

women of childbearing potential should have contraception or negative serum pregnancy test within two weeks before beginning of treatment.

4. Vaginal bleeding.

5. **Decrease male and female fertility.** It is contraindicated in pregnancy as it stimulate uterine contraction and miscarriages.

Mucosal protectives (cytoprotective compounds):

Sucralfate and Bismuth subsalicylate

• **Prevent mucosal injury**

• **Reduce inflammation**

• **Enhance the healing of existing ulcer**

• **Can't be used alone to treat peptic ulcer**

Sucralfate:-

• It is a **complex salt** of **sucrose containing sulfate and poly aluminum hydroxide.**

• **Mechanism :-**

Causes healing of PU by:

1. The **negatively charged sulfate groups bind to the positively charged proteins in the ulcer base**, **forming a protective barrier against acid, bile and pepsin.**

2. **↑ mucus secretion.**

3. ↓ H+ diffusion.

4. ↑ Prostaglandin production.

5. **Binds epidermal and fibroblast growth factors.-->promote healing**

Uses(not alone!!) :-

1. **GU. 2. With NSAID 3. Stress ulcer. 4. Smoker's ulcer.**

Adverse effects of sucralfate

1. **Low bioavailability: 5% absorption orally.**

2. **Active only in gastric acid medium** (forming aluminum and non-absorbable anion), **so if antacids or H2 blockers are given they should be at least I hour apart (after meals).**

3. **Constipation(because of aluminum)**

4. **Dry mouth.(because of aluminum)**

5. **Nausea, vomiting, gastric discomfort and flatulence.**

6. **In renal diseases: aluminum toxicity, osteomalacia and encephalopathy.**

7. **Aluminum Binds some drugs leading to decrease absorption, so given at least 2 hours apart**.

Suralfate is Not commonly used because it has AE

Bismuth subsalicylate:-

- **Part of a quadruple antibiotic therapy regimen in H. pylori-positive ulcers.**
- **Inhibits the activity of pepsin**
- **Increase secretion of mucus**
- **Interact with glycoprotein in necrotic tissue to coat and protect the ulcer**

Treatment of ulcers during pregnancy and lactation

- When peptic ulcer disease is **diagnosed in a pregnant woman** → give acid suppression with **a PPI.**
- **If H. pylori is present, antimicrobial treatment is typically deferred until after delivery**