
peptic ulceration藥物治療新知分享
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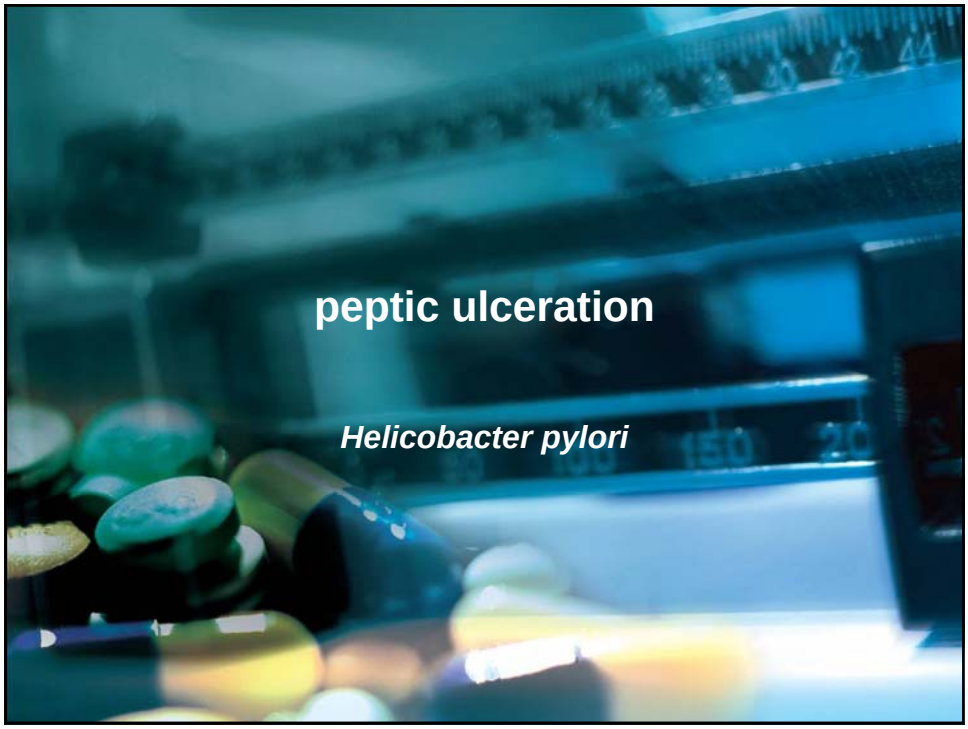
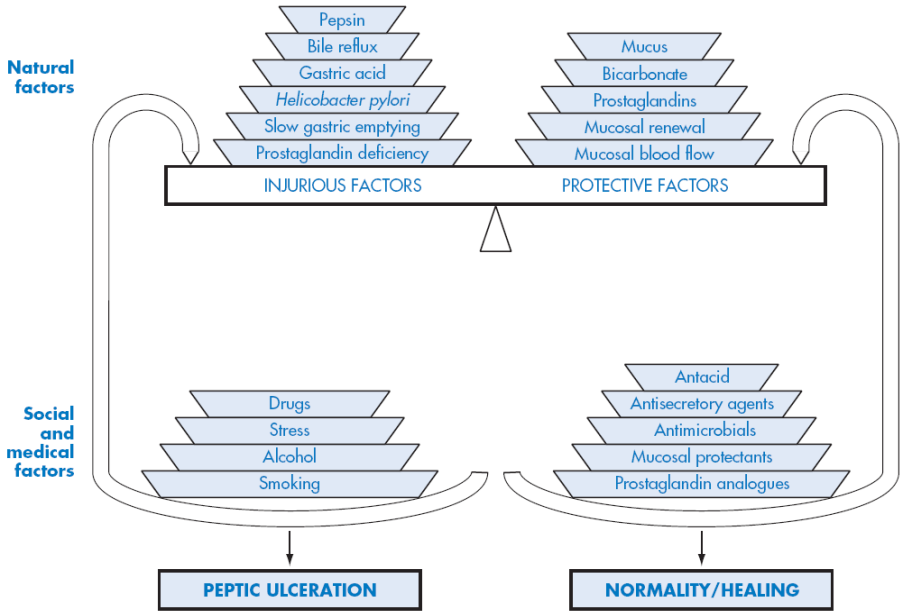
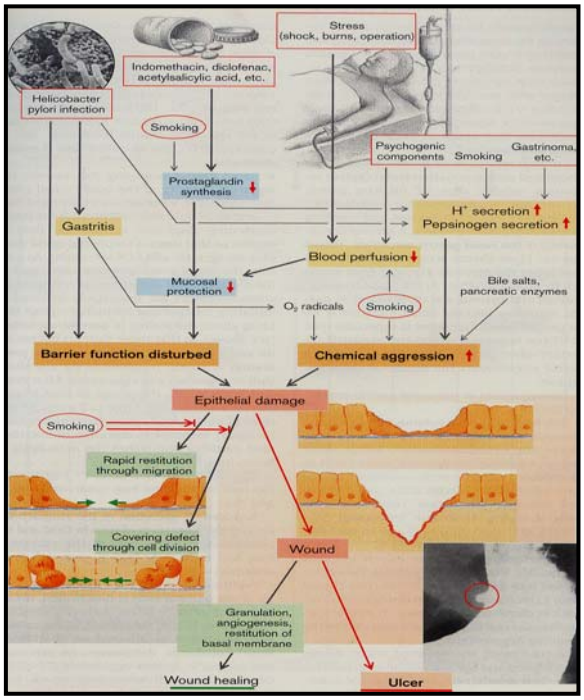
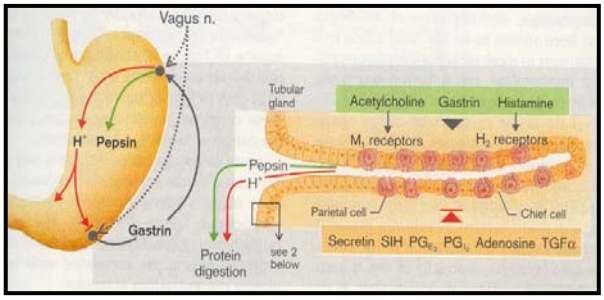
目的
• 讓各位藥師了解目前藥物用於治療胃腸潰瘍的最新資訊，希望能對於藥師在執業上有所助益



Balance between injurious and protective factors in peptic ulceration

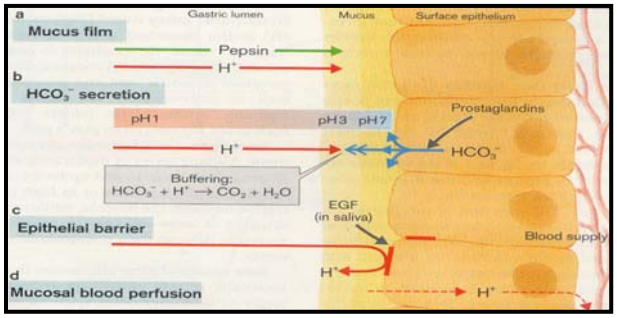




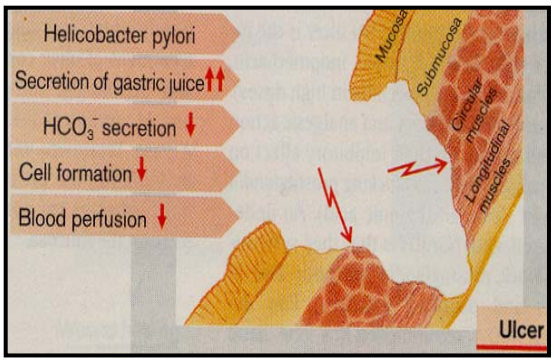


gastric juice secretion

mucosal protection



danger of ulcer



- **definition:**
  an abnormal area of mucosa that has been damaged by the pepsin and hydrochloric acid of gastric juice, with consequent inflammation of the underlying and surrounding tissue
- **etiology**
  - Helicobacter pylori
  - Non-steroidal anti-inflammatory drugs

Investigation

- ***H. pylori*** **is urease (+):**

→ it breaks down urea to carbon dioxide and ammonia, and this property is used to detect its presence

→ the patient takes an oral preparation of carbon-13 urea, and the presence of labelled carbon dioxide in the breath is detected

→ detection of 13C requires samples to be sent to a laboratory with a mass spectrometer

→ the test is very sensitive and specific

Investigation

- **endoscopic biopsy samples can also be examined for the organism microscopically and by culture: these samples are rapidly checked for urease by incubating in a medium containing urea, the production of ammonia being detected by the color change of an indicator (CLO test)**

! *PPIs and bismuth inhibit the bacterial urease and so should be stopped for at least 2 weeks before urease testing*

! recent antibiotic use within 4 weeks, may also give false-negative results

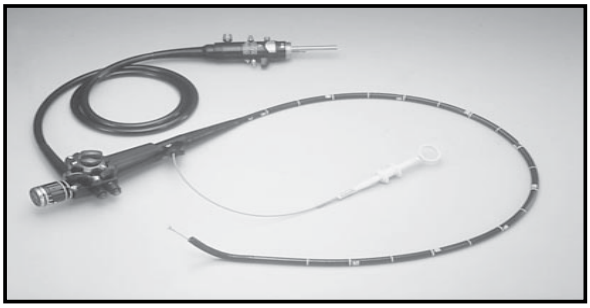
- **an immunoassay for *Helicobacter* antigen in stool samples is widely available and can be used for diagnosis and for monitoring the eradication process**

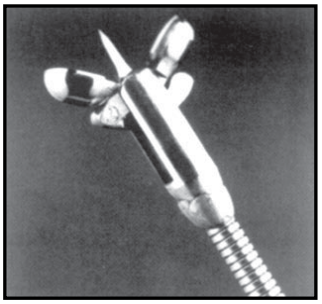
Both the isotopic and CLO tests have about 95% specificity

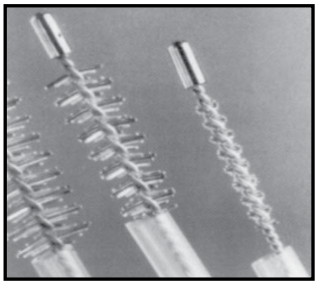
Serology

- an unreliable indicator of infection because of the high carrier rate of *H. pylori* in the general population: 20% of people are carriers by the age of 30, and 50% by the age of 60
- higher carrier rates occur in patients with active gastritis and duodenal ulcer (about 95%) and with gastric ulcer (75%)
- the prevalence rates are falling in the UK, probably because of improving hygiene
- the high rate of gastric cancer in Peru is associated with a 50% prevalence of *H. pylori* in infants from poor families, and 60% of children by age 10 years, whereas juvenile infection is uncommon in the UK and the gastric cancer rate is much lower

fibre-optic endoscope



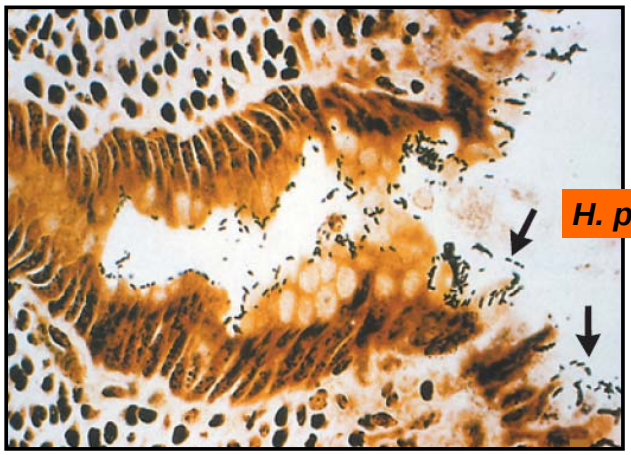




tests for *Helicobacter pylori* Infection

Test	Advantages	Disadvantages
Nonendoscopic		
Serologic test	Widely available; the least expensive of available tests	Positive result may reflect previous rather than current infection; not recommended for confirming eradication
Urea breath test	High negative and positive predictive values; useful before and after treatment	False negative results possible in the presence of PPIs or with recent use of antibiotics or bismuth preparations; considerable resources and personnel required to perform test
Fecal antigen test	High negative and positive predictive values with monoclonal-antibody test; useful before and after treatment	Process of stool collection may be distasteful to patient; false negative results possible in the presence of PPIs or with recent use of antibiotics or bismuth preparations
Endoscopic		
Urease-based tests	Rapid, inexpensive, and accurate in selected patients	False negative results possible in the presence of PPIs or with recent use of antibiotics or bismuth preparations
Histologic assessment	Good sensitivity and specificity	Requires trained personnel
Culture	Excellent specificity; provides opportunity to test for antibiotic sensitivity	Variable sensitivity; requires trained staff and properly equipped facilities

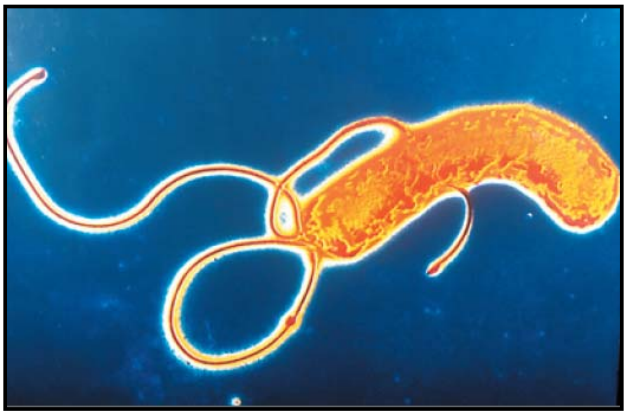
Gastric-Biopsy Specimen Showing *Helicobacter pylori* Adhering to Gastric Epithelium and Underlying Inflammation



Helicobacter pylori

- first identified in the early 1980s
- Gram-negative, multi-flagellate ,spiral, micro-aerophilic bacterium, which appears to be an obligate parasite of gastric epithelium
- found only on gastric epithelium under the mucus layer and on areas of gastric-type epithelium that sometimes occur in the duodenum
- the powerful flagellae that help it to penetrate the mucus, and survives in the hostile gastric environment partly because of the bicarbonate-laden mucus and partly by the action of bacterial urease to produce ammonia
- implicated in: chronic active gastritis, non-ulcer dyspepsia, peptic ulcer, gastric cancer and a rare low-grade lymphoma (MALT [mucosa-associated lymphoid tissue] lymphoma`

Helicobacter pylori



Infection and epigastric symptoms

- ***Helicobacter* infection has not been proven unequivocally to be the prime cause of gastritis and gastro-duodenal ulceration, the circumstantial evidence is very strong:**

✓ gastritis developed in two early research workers with previously normal gastric mucosa after deliberate self-infection

✓ the presence of the organism in 95% of symptomatic patients

✓ resolution of symptoms when the organism is eradicated

✓ eradication of the organism results in longer remissions (up to 4 years in duodenal ulcer disease), than does simple suppression of acid production

Infection and epigastric symptoms

✓ the presence of mucosal changes in asymptomatic carriers, and association with a series of pre-malignant gastric changes

✓ ***H. pylori* causes:**

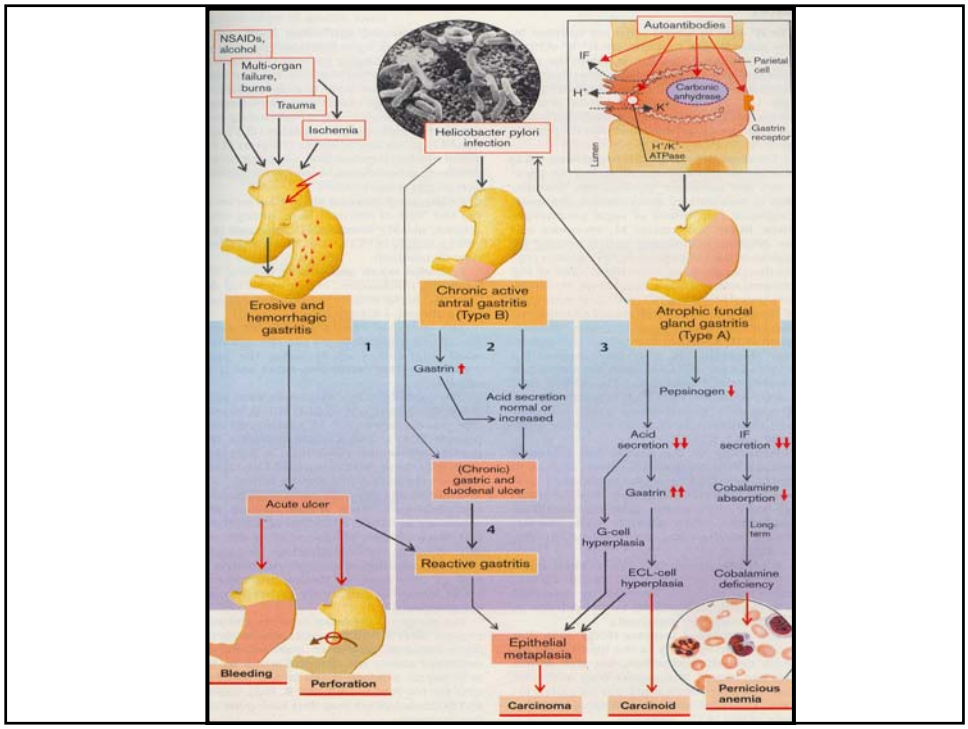
➢ local cytokine release, e.g. IL-6 and IL-8,and so recruitment of inflammatory cells

➢ suppression of somatostatin release and stimulation of histamine levels

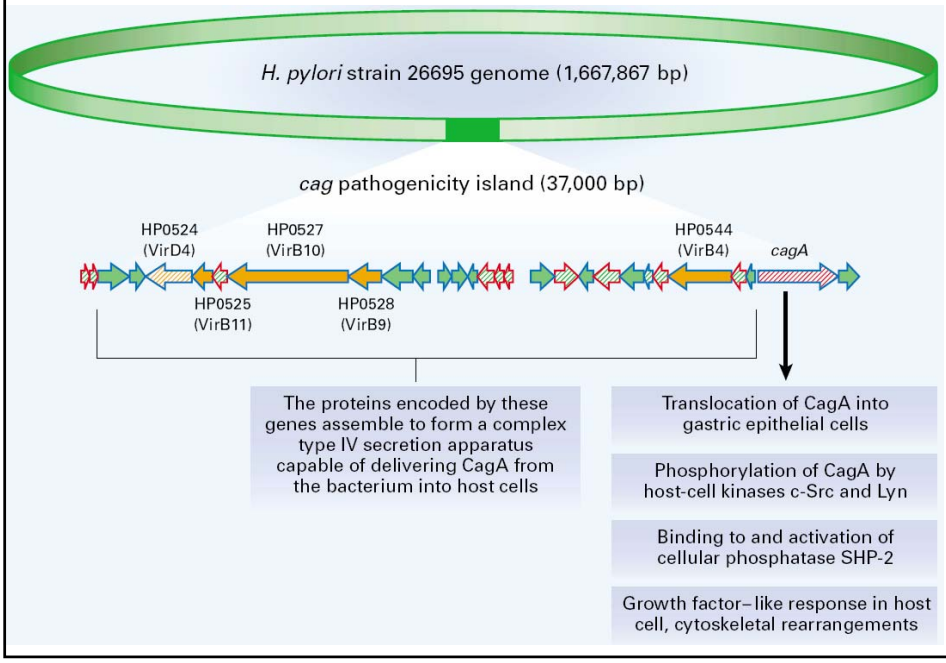
➢ ***the sum of these effects causes increased acid production, which produces gastric meta-plasia in the duodenum, duodenal colonization with H. pylori, and duodenal ulcer***

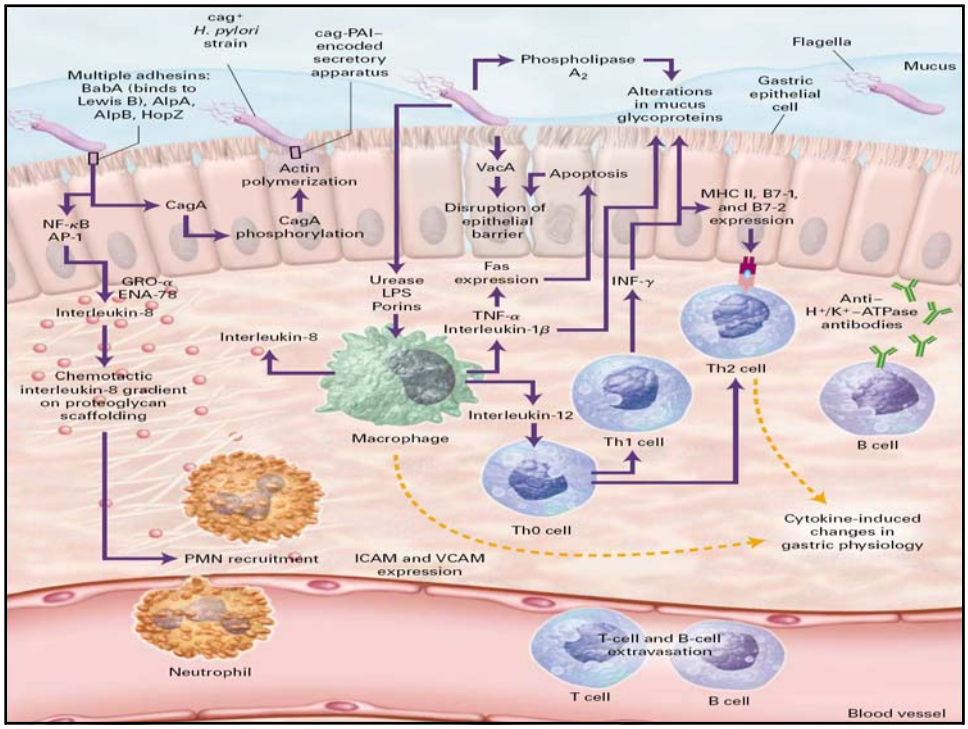
Eradication of H. pylori

- eradication therapy gives a high remission rate in MALT lymphoma

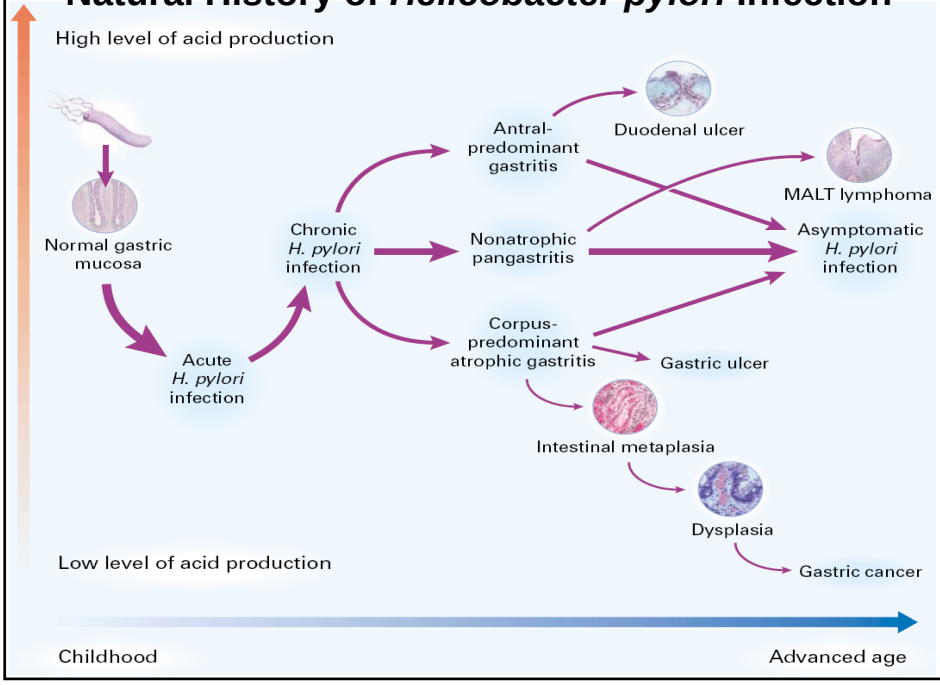


the *cag* pathogenicity Island





Natural History of *Helicobacter pylori* Infection



Eradication of H. pylori

- **Gastric Cancer**
  - extensive epidemiologic data suggest strong associations between *H. pylori* infection and noncardia gastric cancers (i.e., those distal to the gastroesophageal junction)

- the infection is classified as a human carcinogen by the World Health Organization
- the risk of cancer is highest among patients in whom the infection induces inflammation of both the antral and fundic mucosa and causes mucosal atrophy and intestinal metaplasia

- eradication of *H. pylori* infection reduces the progression of atrophic gastritis, but there is little evidence of reversal of atrophy or intestinal metaplasia, and it remains unclear whether eradication reduces the risk of gastric cancer

Guidelines for Evaluation and Management of *Helicobacter pylori* Infection

	American College of Gastroenterology	Maastricht III Consensus Report
Criteria for testing		
	Active gastric or duodenal ulcer, history of active gastric or duodenal ulcer not previously treated for *H. pylori* infection, gastric MALT lymphoma, history of endoscopic resection of early gastric cancer, or uninvestigated dyspepsia	Same as American College of Gastroenterology criteria, with the following additional criteria: gastric cancer in first-degree relative, atrophic gastritis, unexplained iron-deficiency anemia, or chronic idiopathic thrombocytopenic purpura†
Criteria for test-and-treat strategy		
	Age <55 yr and no alarm symptoms§	Age <45 yr and no alarm symptoms‡§
Duration of therapy		
	10–14 Days	7 Days

† Eradication of *H. pylori* in patients with chronic idiopathic thrombocytopenic purpura has been reported to increase the platelet count, although the data are limited.
‡ The age cutoff varies among countries, depending on the prevalence of upper gastrointestinal cancer.
§ Alarm symptoms include dysphagia, weight loss, evidence of gastrointestinal bleeding, and persistent vomiting.

Eradication of H. pylori

- **this is usually using triple therapy with a PPI plus antibiotics, or bismuth chelate plus antibiotics, there are six different, though similar, regimens but none has been proved superior**
- ? it is unclear why a PPI is included as there have been reports of success with antibiotics alone
- ! it may minimize further damage to a pre-existing ulcer and provide superior conditions for ulcer healing
- **dual therapy regimens comprising a PPI and a single antibiotic are not recommended, because resistance is common**

drug regimens for Helicobacter pylori eradication

Treatment for 1–2 weeks with any of the triple regimens given below

Antisecretory		Antibiotic combination
Esomeprazole *or* Pantoprazole *or* Rabeprazole	*PLUS*	Amoxicillin + clarithromycin *or* Clarithromycin + metronidazole
Lansoprazole *or* Omeprazole *or* Ranitidine bismuth citrate	*PLUS*	Amoxicillin + clarithromycin *or* Amoxicillin + metronidazole[a] *or* Clarithromycin + metronidazole

Treatment for 3 days with a quadruple regimen, e.g.

Lansoprazole + clarithromycin + metronidazole + bismuth subcitrate

[a] The combination of amoxicillin and metronidazole is slightly less effective than the others.

eradication of H. pylori

- **one week of triple therapy is usually adequate, but 2 weeks' treatment has eliminated the bacteria in 91% of patients in one trial, with no relapse within a year**
- ✓ these longer regimens are often associated with more side-effect and compliance problems
- ✓ other trials have demonstrated protection against relapse in duodenal ulcer for up to 4 years

- ➢ ***the recommended duration of triple therapy is typically 10 to 14 days in the United States and 7 days in Europe***
- ✓ a recent meta-analysis of 21 randomized trials showed that the rate of eradication increased by :
  - 4 % points with the use of triple therapy for 10 days as compared with 7 days
  - 5 % points with the use of triple therapy for 14 days as compare with 7 days
  - absolute differences that are statistically significant but of marginal clinical significance

Eradication of H. pylori

- ***Amoxicillin*, *nitroimidazole* and *clarithromycin* resistance has been reported, and this is transmissible to other bacteria**

✓ regimens using *amoxicillin* plus either *clarithromycin* or *metronidazole* (some clinicians use *tinidazole*) are suitable for use in the community, but those combining *clarithromycin* or *metronidazole* without *amoxicillin* are best managed by hospital consultants with testing for resistance and eradication on site

✓ resistance testing should preferably be done before treating: this requires endoscopy with biopsy and laboratory culture

Eradication of H. pylori

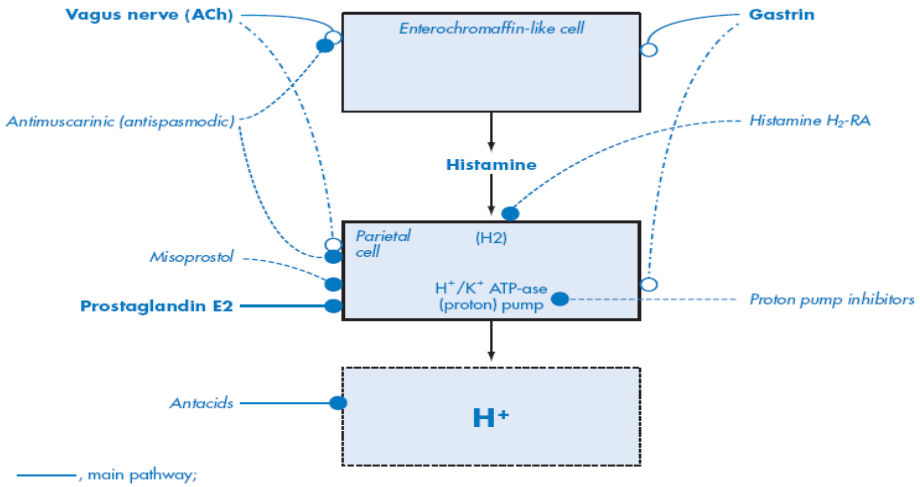
- **mild side-effects are common with regimens containing bismuth, *metronidazole*, *clarithromycin* and *tinidazole*, but side-effects causing cessation of treatment are rare**

✓ *antibiotic-associated colitis is an uncommon side-effect of triple therapy*

- **a 3-day quadruple regimen: a PPI bismuth two antibiotics, is reported to be as effective as 1 week of triple therapy, with fewer side-effects, and a quadruple regimen is also used if a triple regimen fails to eradicate the organism**

should be considered whenever long-term treatment with antisecretory agents is contemplated

Summary of mediators affecting the release of gastric acid and the sites of action of antisecretory drugs and antacids



———, main pathway;
– – – – , subsidiary pathway;
– – – – – – , drug action; ● inhibition/blockade; O stimulation
ACh, acetylcholine (M-receptor); H2, histamine H2 receptor.
Misoprostol enhances the secretion of bicarbonate and mucus, which are cytoprotective, and reduces acid secretion.

Eradication of H. pylori

- **another possible initial therapy in areas with a high prevalence of clarithromycin-resistant *H. pylori* infection (i.e., >20%) is quadruple therapy comprising the use of a proton-pump inhibitor, tetracycline, metronidazole, and a bismuth salt for 10 to 14 days; however, bismuth salts are not available in some countries, including the United States**

- ✓ a recent meta-analysis of 93 studies showed a higher rate of eradication with quadruple therapy that included both clarithromycin and metronidazole than with triple therapy that included both these agents in populations with either clarithromycin or metronidazole resistance

Eradication of H. pylori

- **alternative initial regimen is 10-day sequential therapy, involving a proton-pump inhibitor plus amoxicillin for 5 days followed by a proton-pump inhibitor plus clarithromycin and tinidazole for 5 more days**

- ✓ this regimen was reported to achieve an eradication rate of 93%,as compared with a rate of 77% with standard triple therapy, in a meta-analysis of 10 randomized trials in Italy

- ✓ in a trial in Spain, the eradication rate among patients randomly assigned to receive sequential therapy was only 84%, indicating a need to confirm its efficacy before it is used widely

Standard initial treatment (use one of the following three options)

Triple therapy for 7–14 days
- PPI, healing dose twice/day*
- Amoxicillin, 1 g twice/day†
- Clarithromycin, 500 mg twice/day

Quadruple therapy for 10–14 days‡
- PPI, healing dose twice/day*
- Tripotassium dicitratobismuthate, 120 mg four times/day
- Tetracycline, 500 mg four times/day
- Metronidazole, 250 mg four times/day§

Sequential therapy
- Days 1–5
  - PPI, healing dose twice/day*
  - Amoxicillin, 1 g twice/day
- Days 6–10
  - PPI, healing dose twice/day*
  - Clarithromycin, 500 mg twice/day
  - Tinidazole, 500 mg twice/day§

Second-line therapy, if triple therapy involving clarithromycin was used initially (use one or the other)

Triple therapy for 7–14 days
- PPI, healing dose once/day*
- Amoxicillin, 1 g twice/day
- Metronidazole, 500 mg (or 400 mg) twice/day§

Quadruple therapy, as recommended for initial therapy

* Examples of healing doses of proton-pump inhibitors (PPIs) include the following regimens, all twice per day: omeprazole at a dose of 20 mg, esomeprazole at a dose of 20 mg, rabeprazole at a dose of 20 mg, pantoprazole at a dose of 40 mg, and lansoprazole at a dose of 30 mg. In some studies, esomeprazole has been given at a dose of 40 mg once per day.

† If the patient has an allergy to amoxicillin, substitute metronidazole (at a dose of 500 mg or 400 mg) twice per day and (in initial triple therapy only) use clarithromycin at reduced dose of 250 mg twice per day.

‡ Quadruple therapy is appropriate as first-line treatment in areas in which the prevalence of resistance to clarithromycin or metronidazole is high (>20%) or in patients with recent or repeated exposure to clarithromycin or metronidazole.

§ Alcohol should be avoided during treatment with metronidazole or tinidazole, owing to the potential for a reaction resembling the reaction to disulfiram with alcohol use.

Eradication of H. pylori

- **Confirmation of Eradication**
- ✓ in patients who have had an *H. pylori*–associated ulcer or gastric MALT lymphoma or who have undergone resection for early gastric cancer
- avoid repeated treatment of patients whose symptoms are not attributable to *H. pylori,* follow-up testing is indicated in patients whose symptoms persist after *H. pylori* eradication treatment for dyspepsia
- ✓ by means of a urea breath test or fecal antigen test; these are performed 4 weeks or longer after completion of therapy, to avoid false negative results due to suppression of *H. pylori*
- ✓ can also be confirmed by testing during repeat endoscopy for patients in whom endoscopy is required

Eradication of H. pylori

- **Management of Persistent Infection after Treatment**
- ➢ first: to confirm that the infection is still present and consider whether additional antimicrobial treatment is appropriate
- ➢ further attempts at eradication are indicated in patients with confirmed ulcer or gastric MALT lymphoma or after resection for early gastric cancer
- ➢ if the initial therapy was for uninvestigated dyspepsia, which is associated with a low likelihood of underlying ulcer and symptomatic benefit from eradication, the appropriateness of further eradication therapy is unclear; data from studies designed to determine the optimal management of such cases are lacking

Eradication of H. pylori

- options for treatment include empirical acid-inhibitory therapy, endoscopy to check for underlying ulcer or another cause of symptoms, and repeat use of the noninvasive test-and treat strategy

- the possibility that symptoms may be due to a different cause (e.g., biliary tract, pancreatic, musculoskeletal, or cardiac disease or psychosocial stress) should routinely be considered

- if another course of therapy is administered to eradicate *H. pylori* infection, the importance of adherence to the treatment regimen should be emphasized, since poor adherence may underlie the failure of initial therapy

Eradication of H. pylori

- **the choice of second-line treatment is influenced by the initial treatment:**
- treatment failure is often related to *H. pylori* resistance to clarithromycin or metronidazole (or both agents)
- if initial therapy did not include bismuth salt, bismuth-based quadruple therapy is commonly used as second-line therapy, with eradication rates in case series ranging from 57 to 95%
- triple therapies have also been tested as second-line therapies in patients in whom initial therapy failed

- a proton-pump inhibitor used in combination with metronidazole and either amoxicillin or tetracycline is recommended in patients previously treated with a proton-pump inhibitor, amoxicillin, and clarithromycin
- clarithromycin should be avoided as part of second-line therapy unless resistance testing confirms that the *H. pylori* strain is susceptible to the drug

Eradication of H. pylori

- **several regimens have been reported to be effective as salvage therapy in case series**

✓ for example, re-treatment after treatment failure with a triple regimen consisting of levofloxacin or rifabutin, along with a proton-pump inhibitor and amoxicillin, has been associated with high rates of eradication

- caution is warranted in the use of rifabutin, which may lead to resistance of mycobacteria in patients with preexisting mycobacterial infection

NSAID-induced ulceration and H. pylori infection

? **the nature of the ulcerogenic interaction between *H. pylori* and NSAIDs is unclear**

✓ NSAID induced ulcers are more likely to bleed than those caused by *H. pylori*, possibly because the organism stimulates the production of gastro-protective PGE2, whereas NSAIDs cause inhibition of PG production

✓ *H. pylori* eradication reduces the risk of new NSAID-induced ulcers in patients who have not had previous ulceration, the situation is less clear in those with pre-existing ulceration

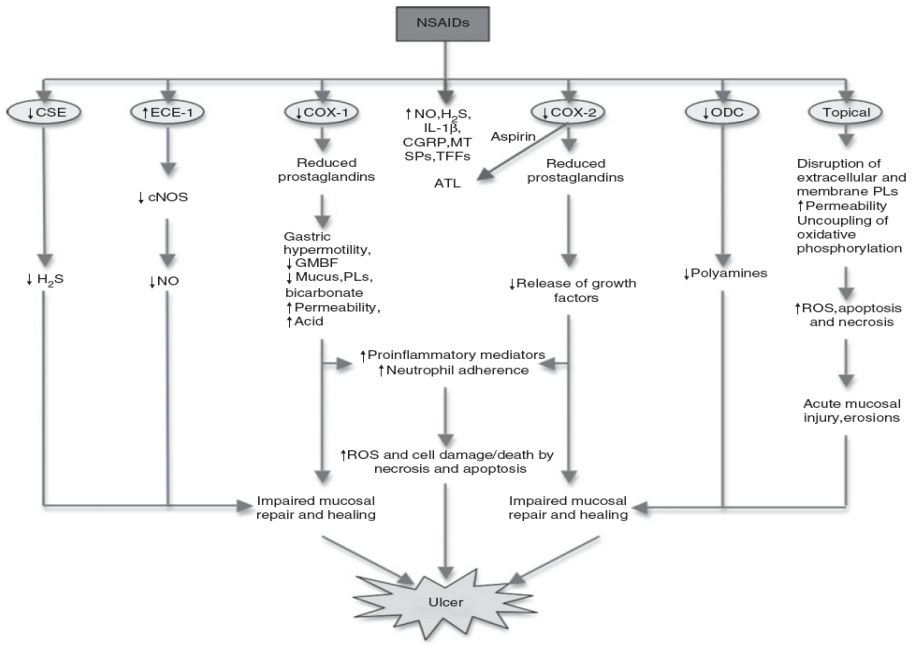
NSAID-induced ulceration and H. pylori infection

- **one study has shown that in patients with NSAID-induced symptomatic gastric ulcers, suppression of acid production with *omeprazole* is probably adequate**

- if there is a proven history of peptic ulceration and *H. pylori* infection, eradication before initiating essential NSAID treatment may reduce the risk of new ulcers

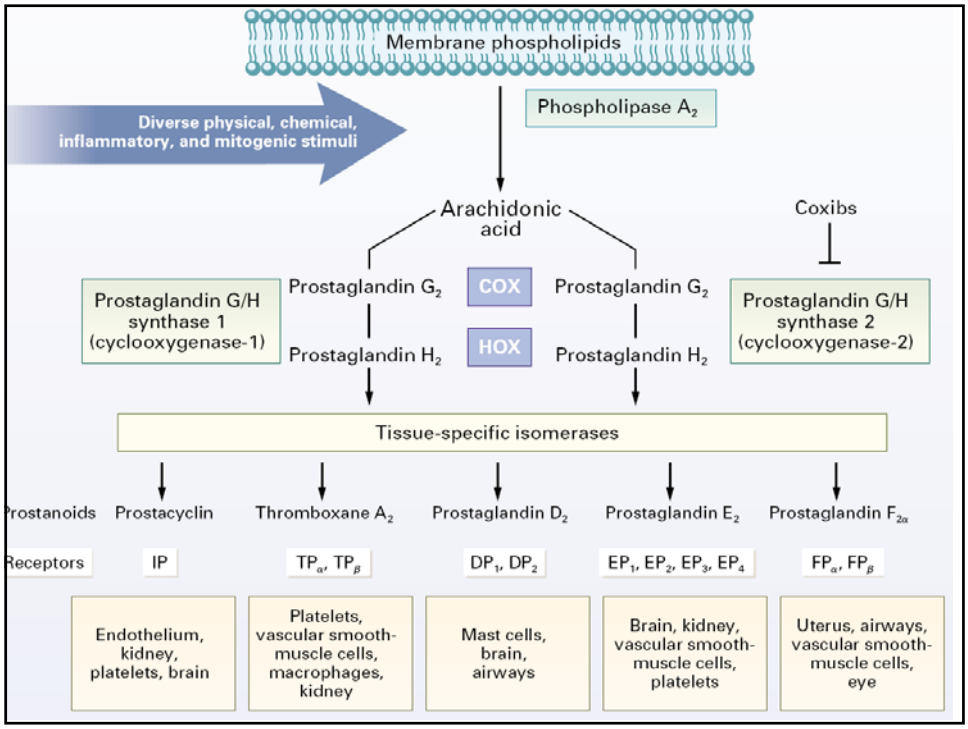
- none of this applies to patients taking low-dose *aspirin*

Cellular and molecular pathogenesis of NSAID-induced ulcers

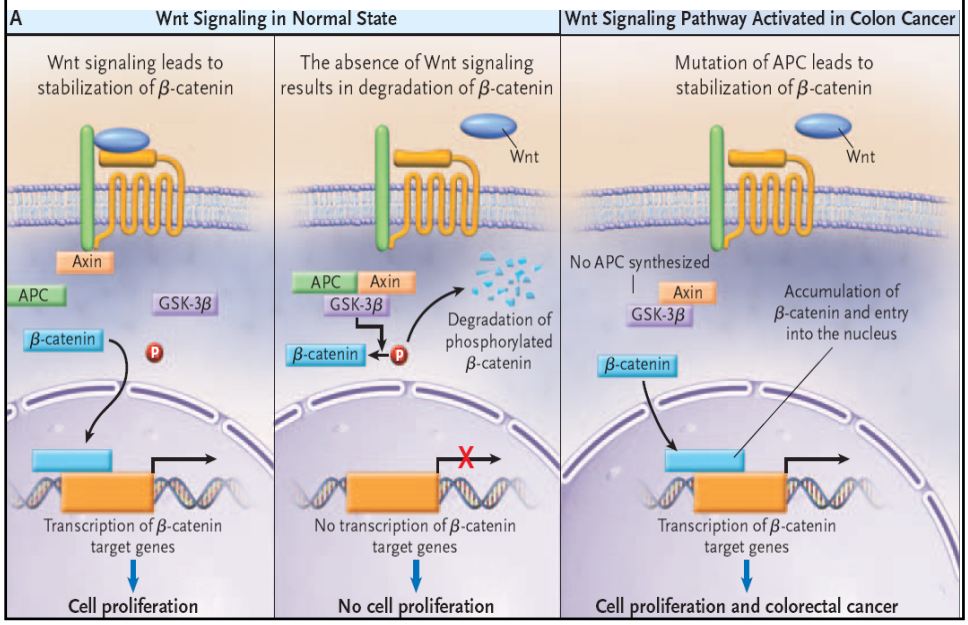


Potential mechanisms of NSAID-induced apoptosis in the pathogenesis of gastrointestinal ulcers

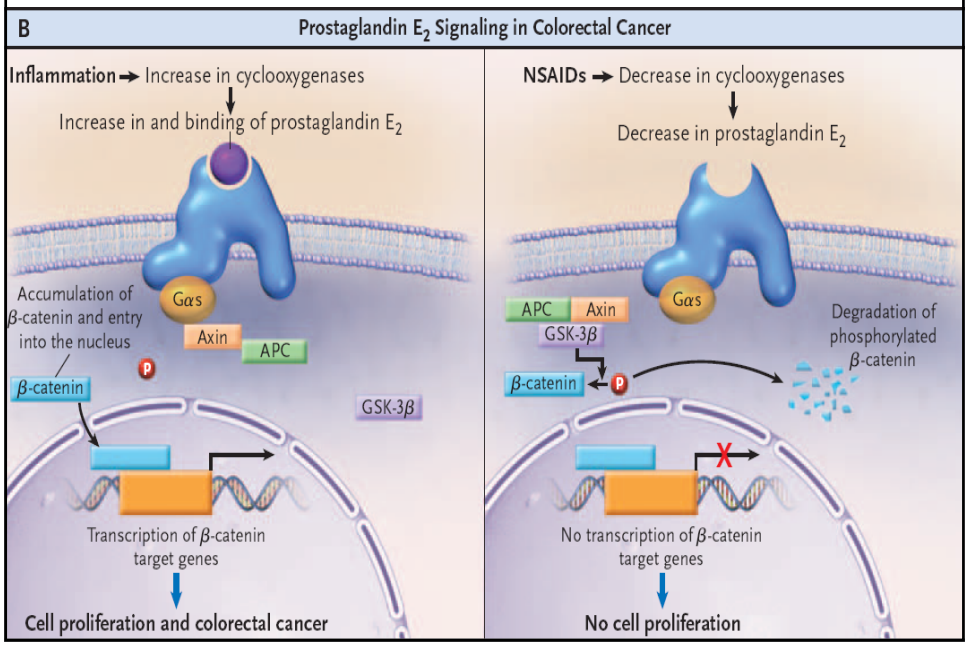
Protein	Abbreviation	Function	NSAID effect	Mechanism of apoptosis
Tumour necrosis factor alpha	TNF-α	Induces apoptosis when bound to TNFR I and II	Upregulates levels	Direct activation of effector caspases or indirect activation of mitochondrial apoptotic pathway
Caspase 8		Initiator caspase	Activation	Cytochrome c release and sequential activation of caspases-9, and effector caspases
Caspase 9		Initiator caspase	Activation	Activation of effector caspases Mediates Smac-induced apoptosis
Cytochrome c		Promotes apoptosis	↑ Release via ↑mitochondrial permeability	Sequential activation of initiator caspase-9 and effector caspases
Second mitochondria-derived activator of caspase	Smac	Promotes apoptosis	Induces release	Activation of effector caspases
Apoptosis inducing factor	AIF	Promotes caspase-independent apoptosis	↑ Release via ↑mitochondrial permeability	Caspase-independent apoptosis-like cell death
Nuclear factor kappa-B	NF-κB	Promotes cell survival	Inhibit activation	Activation of effector caspase-3
Survivin		Apoptosis inhibitor	↓ Levels	↑ Effector caspase-3 mediated apoptosis ↑ Caspase-independent apoptosis
Ubiquitin proteosome system	UPS	Promotes cell survival	↓ Proteosome activity	Activation of caspase- 9 and effector caspase-3
Protein kinase C-β1	PKC-β1	Promotes cell survival	Downregulates expression	↓ Cell survival
Poly (ADP-ribose) polymerase	PARP	Mediates DNA repair	Cleavage	Enables effector caspase-3
C/EBP homologous protein	CHOP	Controls development of apoptosis in response to ER stress	Upregulates expression	Initiates apoptotic response



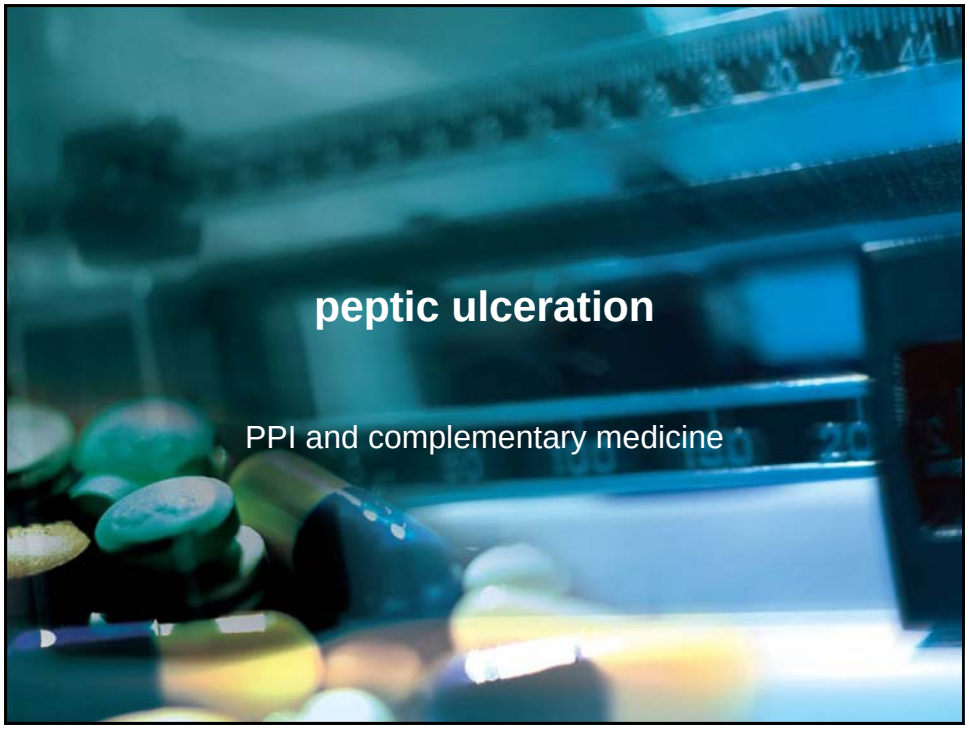
Colorectal Cancer: One Pathway, Two Stimuli



Colorectal Cancer: One Pathway, Two Stimuli



Gastroprotective effect	Receptor/s (species)	COX-Isoform
Inhibit acid secretion	EP_3 (mouse, rat) IP (mouse)	COX-1
Stimulate acid secretion	EP_4 (rat)	
Stimulate mucus secretion	EP_4 (rat)	
Stimulate bicarbonate secretion in stomach	EP_1 (rat, mouse)	COX-1
Stimulate bicarbonate secretion in duodenum	EP4 (rat, human)	
Maintain mucosal surface hydrophobicity	? (mouse)	COX-1
Increase GMBF	$EP_2/EP_3/EP_4$ (rat), EP_1 (mouse)	COX-1
Facilitate CGRP-mediated hyperaemic response	EP_2, IP (rat)	
Suppress increased TNF-α expression	EP_2, EP_4 (mouse)	COX-2
Inhibit neutrophil adherence and activation	EP_2/EP_4	COX-2
Inhibit epithelial cell apoptosis	EP_2/EP_4 (guinea pig)	
Decrease gastric hypermotility	EP_1 (rat)	COX-1
Decrease epithelial paracellular permeability	? (rat)	COX-1
Adaptive gastric cytoprotection	EP_1 (rat, mouse)	
Accelerate restitution	? (rat, mouse)	COX-1, COX-2
Accelerate ulcer healing	EP_4 (mouse)	COX-2
Resist ischaemia /reperfusion induced gastric damage	IP	COX-2



topic

- long-term safety concerns with protonpump inhibitors
- safety of concomitant use of proton pump inhibitors and clopidogrel
- gastric acidity inhibitors and the risk of intestinal infections

- probiotics and peptic ulceration