Potential Causes of Dyspepsia

Dyspepsia	A non specific term, encompasses a number of symptoms attributable to the upper GI tract.
Oesophagitis	Gastro oesophageal reflux disease (GORD). Barrett's oesophagus
Gastritis	Type: A,B,C
Peptic Ulcers	Gastic ulcers. Duodenal ulcers
Zollinger-Ellison syndrome	a rare condition caused by tumors (gastrinomas) that produce excessive gastrin, leading to overproduction of stomach acid and peptic ulcers.
Gastric Cancer	

3 categories of Gastritis

Type A - AUTOIMMUNE	(antibodies against parietal cells). Reduced or no acid secretion and intrinsic factor. Aplastic anaemia due to Vit B12 deficiency.
Type B - BACTERIAL	*Helicobacter pylori* infection. Elevated acid secretion

3 categories of Gastritis (cont)

Type C - CHEMICAL	Chemicals/drugs eg aspirin. Elevated acid secretion

Diet & Lifestyle & Other drugs

Other causes of Dyspepsia

Caffeine:	PDE inhibitor promotes acid secretion
Alcohol:	Dissolves mucous layer
Spicy Food:	Capsaicin, Activates TRPV1 but may inhibit acid secretion via vagal inactivation.
Concomitant medication (drugs that can relax LOS):	PDEV inhibitors eg sildenafil like drugs. Nitrates (relaxes LOS via PDE activation). Theophylline (Relaxes LOS via PDE inhibition). Drugs with antimuscarinic properties (block muscarinic receptors). Ca2+ channel blockers (prevent calcium entry).
Obesity and pregnancy	increased intra--abdominal pressure causing reflux.

The Oesophagus

The mucosa of the oesophagus is non-keratinzed stratified squamous epithelium

The type of muscle in the muscularis of the oesophagus varies by region	the superior 1/3 is skeletal muscle, the intermediate 1/3 is skeletal and smooth muscle, the inferior 1/3 is smooth muscle.

The Oesophagus (cont)

Adventitia replaces serosa.	**Serosa** = a slick covering that helps organs move smoothly (like the outer wrap of your intestines). **Adventitia** = a rougher outer layer that holds the organ in place, usually found where organs are attached to other tissues (like parts of the esophagus or rectum). Meaning that part of the organ is not freely moving inside a cavity anymore, but rather fixed or connected to surrounding structures.

Type A Gastritis

Destruction of parietal cells	Reduced or absent acid secretion. Vitamin B12 deficiency. Anaemia

Type A Gastritis (cont)

Other conditions associated with Type A Gastritis	**Autoimmune thyroiditis** (Hashimoto's disease). **Type I Diabetes. Addison's Disease** (Adrenal glands, reduced cortisol & aldosterone). **Vitiligo** (skin pigmentation disorder) white patches of skin.
Treatment potentially required	Hydroxocobalamin injections

Type C Gastritis - Chemical, Drug and Diet

SAID's	Steroidal anti-inflammatory drugs (SAID's) inhibit phospholipase A2 by promoting expression of annexin 1 and suppressing expression of COX-2.
NSAID's	Non-steroidal anti-inflammatory drugs inhibit the cyclo-oxygenase enzymes. **COX-1 COX-2**

Barrett's Oesphagus

Long-standing reflux of acid

About 1 in 10 people with GORD develop Barrett's oesophagus.

Normal stratified squamous epithelium is replaced with simple columnar epithelium with goblet (mucus cells)

Acid Secretion

M3 and CCK2 (CCKB; gastrin) receptors	GTP-binding protein coupled receptor (GPCR). Linked to Gq (stimulates Phospholipase C). Increases intracellular Ca2+ via PIP2 conversion to DAG & IP3.
H2 receptors	GTP-binding protein coupled receptor (GPCR) Linked to Gs (stimulates adenylate cyclase) Increases intracellular cAMP
Inhibit or Reduce acid secretion:	Proglumide, Misoprostol, H2 Blockers, Atropine, Proton Pump Inhibitors.

Type B Gastritis - Helicobacter pylori

Associated with:	80% of gastric ulcers. 95-100%. of duodenal ulcers. 100% chronic antral gastritis. gastric cancer (younger infected, greater chance)
Gram negative spiral bacterium	colonises mucus in both stomach and duodenum.

Type B Gastritis - Helicobacter pylori (cont)

Secretes	urea from high urease activity (antral pH raised, gastrin & acid secretion increases). PAF (platelet activating factor).
Gram negative	Doesn't retain Crystal Violet stain! - **Pink stain!!!**

Eradication of H.pylori

First Line treatment	ONE WEEK TWICE DAILY Amoxycillin 300mg **and either** Clarithromycin 500 mg **or** Metronidazole 400 mg **and either** omeprazole 20 mg **or** lansoprazole 30 mg.
	Consider lowest acquisition costs and previous exposure to clarithromycin or metronidazole!
If allergic to penicillin ONE WEEK TWICE DAILY	Clarithromycin 500 mg Metronidazole 400 mg **and either** Omeprazole 20 mg **or** lansoprazole 30 mg

Eradication of H.pylori (cont)

If allergic to penicillin and previous exposure to clarithromycin and metronidazole ONE WEEK TWICE DAILY	Tetracycline 1g and metronidazole 400 mg. Bismuth subsalicylate and omeprazole 20 mg

Mucosa aggressors and protectors

Protective	Mucus, Prostaglandins, Bicarbonate, Mucosal blood flow
Aggressive	Acid, Pepsin, NSAID's, *H. pylori*, Drugs, Diet

Treatment for Dyspepsia

Surgery (1900--1970's)	Gastric vagotomy & antacids
Drugs (1970's onwards)	
Barriers/-Protection:	Alginate and Sucralfate-antacid and barrier
Muscarinic cholinergic receptor antagonists (M3)	Pirenzepine
Selective H2 receptor antagonists	Cimetidine, ranitidine, famotidine
Drugs (1990's onwards)	
Proton Pump Inhibitors	Omeprazole, Pantoprazole, Lansoprazole, Rabeprazole and Esomeprazole

protecting gastric mucosa when taking NSAID's	
Synthetic PGE2	Misoprostol + NSAID. Problem – smooth muscle relaxation – diarrhoea.
Antacids eg: TUMS, Rennie.	Inhibit acid secretion: **H2 antagonists** eg: famotidine. **Proton Pump Inhibitors (PPI's)** eg omeprazole, lansoprazole, esomeprazole, pantoprazole.
Selective COX-II inhibitors	Diclofenac, refocoxib (Vioxx)
Emerging novel NSAIDS (not clinically used)	NO-flurbiprofen (nitric oxide releasing derivatives). H2S releasing NSAID's (currently awaiting MAA)