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Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Acute treatment of variceal haemorrhage

• ABC: patients should ideally be resuscitated prior to endoscopy • correct clotting: FFP, vitamin K
• vasoactive agents:
 terlipressin is currently the only licensed vasoactive agent and is supported by NICE guidelines.
 powerful splanchnic vasoconstrictor
 It has been shown to be of benefit in initial haemostasis and preventing rebleeding.
 the most appropriate treatment whilst awaiting urgent endoscopy
 As a vasoconstrictor its administration is contraindicated in those with a history of ischaemic heart disease as it may precipitate myocardial ischaemia. Octreotide may also be used although there is some evidence that terlipressin has a greater effect on reducing mortality • prophylactic antibiotics
 have been shown in multiple meta-analyses to reduce mortality in patients with liver cirrhosis.
 Quinolones are typically used. • endoscopy:
 endoscopic variceal band ligation is superior to endoscopic sclerotherapy. NICE recommend band ligation • Sengstaken-Blakemore tube if uncontrolled haemorrhage Balloon tamponade (for example, using a Sengstaken-Blakemore tube) may be used as a holding measure in situations where, for whatever reason, a definitive procedure cannot be performed to control bleeding (for example, endoscopy or transjugular intrahepatic portosystemic shunting).
 It is generally very effective in achieving control of variceal bleeding. • Transjugular Intrahepatic Portosystemic Shunt (TIPSS) if above measures fail Prophylaxis of variceal haemorrhage • propranolol:
 reduced rebleeding and mortality compared to placebo • endoscopic variceal band ligation (EVL)
 is superior to endoscopic sclerotherapy.
 It should be performed at two-weekly intervals until all varices have been eradicated.
 Proton pump inhibitor cover is given to prevent EVL-induced ulceration Prognosis • Overall mortality from bleeding varices is around 30%

Esophageal Rupture
• Causes
 Iatrogenic esophageal perforation:
 most common cause of esophageal perforation Generally injury during upper endoscopy Symptoms usually within 24 hours of endoscopy Foreign body ingestion Trauma

Malignancy Boerhaave syndrome

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 Severe vomiting/increased intrathoracic pressure → rupture of all layers of the esophageal wall In > 90% of cases, the rupture occurs in the distal third of the esophagus on the left dorsolateral wall surface. Sex: ♂ > ♀ (3:1) Associations Excessive intake of alcohol or food in the recent past Repeated episodes of vomiting Childbirth Seizures Prolonged coughing Weightlifting • Feature: Mackler's triad (vomiting, chest pain and surgical emphysema) is classical but absent in almost half the cases. surgical emphysema Subcutaneous emphysema → crepitus in the suprasternal notch mediastinal emphysema →"crunching" or "crackling" sound on chest auscultation (Hamman's sign) The most relevant finding on examination is the crepitus over the chest Dyspnea, cyanosis • investigations: Gastrografin swallow will confirm the site of perforation in approximately 65-75% of cases, and is the recommended first line investigation. chest x ray useful in the initial diagnosis The most common finding is a unilateral effusion, usually on the left. Because the most perforations occur in the left posterior aspect of the esophagus. Other findings may include pneumothorax, hydropneumothorax, pneumomediastinum, surgical emphysema. mediastinal widening. Lateral neck x rays may be useful in the early stages where the diagnosis is uncertain and surgical emphysema is not seen on a plain CXR. CT scan: indicated in unstable/uncooperative patients, pneumoperitoneum on x-ray, or ifx-rays and contrast esophagram are inconclusive Barium swallow more sensitive at 90% for detecting small perforations but carries the risk of a severe inflammatory response (mediastinaitis). • Prognosis A reported mortality estimate is approximately 35%, making it the most lethal perforation of the GI tract. If intervention is delayed longer than 24 hours, the mortality rate (even with surgical intervention) rises to higher than 50% and to nearly 90% after 48 hours. Left untreated, the mortality rate is close to 100%.

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Hiccup
• caused by frequent or rhythmic clonic contraction of the diaphragm. • When prolonged, other causes should be considered including: CNS disease - posterior fossa tumour, brain injury, encephalitis Phrenic nerve or diaphragm irritation - tumour, pleurisy, pneumonia, intrathoracic adenopathy, pericarditis, gastro-oesophageal reflux, oesophagitis Systemic causes include alcohol intoxication and uraemia. Other causes include foreign body or insect in the ear. In infants it may be associated with apnoea or hyperventilation. • Treatment Folk remedies include aerophagia, breath holding, pharyngeal stimulation, distraction. Haloperidol, metaclopramide and several anaesthetic agents are also said to work.

Gastric conditions

Helicobacter pylori

Overview • Helicobacter pylori is a Gram negative bacteria associated with a variety of gastrointestinal problems, principally peptic ulcer disease

Associations • Peptic ulcer disease (95% of duodenal ulcers, 75% of gastric ulcers) • gastric cancer (≈ 5%)
 The most common location is the lesser curvature. appears as an ulcer with heaped-up margins. • B cell lymphoma of MALT tissue (eradication of H pylori results causes regression in 80% of patients) • Atrophic gastritis

Helicobacter pylori is NOT associated with GORD • The is no apparent role of H pylori in Gastro-oesophageal reflux disease (GORD) • there is currently no role in GORD for the eradication of H pylori

Diagnosis

Gastroenterology

Noninvasive methods

Urea breath test • The preferred method for initial diagnosis or confirmation of eradication • sensitivity 95-98%, specificity 97-98% • should not be performed within 4 weeks of treatment with an antibacterial or within 2 weeks of an antisecretory drug (e.g. a proton pump inhibitor)

Serum antibody • sensitivity 85%, specificity 80% • remains positive after eradication (cannot distinguish between a past and current infection.)

Stool antigen test • Sensitivity 90%, specificity 95% • Can be used for initial diagnosis BUT NICE guidelines do not recommend its use to confirm eradication due to a lack of evidence. Invasive methods Rapid urease test (e.g. CLO test) • Performed on biopsy tissue obtained during endoscopy • Detects the amount of ammonia produced by H. pylori during urea hydrolysis • Sensitivity 93-97%, specificity 95-98% • the false negative rate increases significantly in: recent gastrointestinal haemorrhage,
 acid suppression therapy and
 recent antibiotic treatment.

Culture of gastric biopsy (Gold standard) • sensitivity 70%, specificity 100% • Staining and direct microscopic identification (silver stain) • Curved, gram-negative rods with multiple flagella is the typical appearance of H.pylori.

Gastric biopsy
• Histological evaluation alone, no culture • Sensitivity 95-99%, specificity 95-99%

Test to confirm eradication : • When to test for complete eradication? Re-testing for Helicobacter pylori is indicated only in the setting of peptic ulcer disease to confirm eradication where an initial

test is positive. • Which test? Carbon-13 urea breath testing is the only well validated method for confirming the successful eradication of Helicobacter pylori.

PPIs should be discontinued at least 2 weeks prior to most H. pylori testing modalities to minimize rates of false-negative results. However, some testing modalities, e.g., histology, are not affected by recent PPI treatment.

Management
• First-line treatment Not allergic to penicillin → PPI + amoxicillin + either clarithromycin or metronidazole. Allergic to penicillin → PPI + metronidazole + clarithromycin Allergic to penicillin + previous exposure to clarithromycin → PPI + bismuth + metronidazole + tetracycline

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• Re-testing for H. pylori Re-testing for H. pylori before second-line treatment is considered to confirm eradication as there are serious side effects associated with antibiotics, e.g. Clostridium difficile infection, and antibiotic resistance is increasing.
 Eradication therapy is effective in 80-85% of cases and should not be repeated without evidence of treatment failure.

 the carbon-13 urea breath test is the most accurate method of re-testing for H. pylori.

 NICE guidelines 2019 state: Perform re-testing for H pylori using a carbon- 13 urea breath test. (There is currently insufficient evidence to recommend the stool antigen test as a test of eradication)

• Second-line treatment (If still symptomatic after first-line + positive re-testing for H. pylori) Not allergic to penicillin → PPI + amoxicillin + either clarithromycin or metronidazole (whichever was not used first-line) If there is a previous exposure to clarithromycin and metronidazole →PPI + amoxicillin + quinolone or tetracycline (whichever has the lowest acquisition cost).
 Allergic to penicillin + NO previous exposure to a quinolone → PPI + metronidazole + levofloxacin Allergic to penicillin + previous exposure to a quinolone → PPI + bismuth + metronidazole + tetracycline.

Peptic ulcer Basic Bleeding from Posterior duodenal ulcers are due to erosion of the gastroduodenal artery

• The right and left gastroepiploic arteries (gastro-omental arteries) supply the greater curvature of the stomach. The source of ulcer bleeding in the greater curvature of the stomach Left gastroepiploic artery
• The right gastric artery arises from the hepatic artery or the left hepatic artery, supplies the pylorus and travels along the lesser curvature of the stomach, supplying it, and anastomosing with the left gastric artery.
 the cause of ulcer bleeding in the lesser curvature of the stomach right gastric artery • The pancreaticoduodenal artery (a branch of the gastroduodenal artery) supplies mainly the upper and

lower duodenum and the head of the pancreas. • The right hepatic artery supplies the right lobe of the liver and part of the caudate lobe. The golden notes Sources of bleeding in peptic ulcers: • greater curvature of the stomach Left gastroepiploic artery • lesser curvature of the stomach right gastric artery • Posterior duodenal ulcers gastroduodenal artery pancreaticoduodenal artery (a branch of the gastroduodenal artery) supplies mainly the upper and lower duodenum.

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The golden notes Sites of peptic ulcers: • 80% are duodenal.
• The most common site near the pylorus, on the duodenal side
• The less frequent site lesser curvature of stomach or at the point at which the esophagus enters the stomach.

Risk factors for peptic ulceration include • Helicobacter pylori (H. pylori) infection,
• non-steroidal anti-inflammatory drug (NSAID) use,
• cigarette smoking and
• genetic factors - Lewis blood group antigens facilitate H. pylori attachment to the mucosa.

Interventions for peptic ulcer disease (NICE 2012) • peptic ulcer + H pylori H pylori eradication therapy • peptic ulcer + H pylori retesting for H pylori 6 to 8 weeks after beginning treatment, • gastric ulcer + H pylori repeat endoscopy 6 to 8 weeks after beginning treatment • In people at high risk (previous ulceration) and for whom NSAID continuation is necessary, consider a COX-2 selective NSAID instead of a standard NSAID with a PPI. The Two highly selective or specific in their ability to inhibit COX-2 while having little or no COX-1 affinity are rofecoxib and celecoxib.
• Offer H2RA therapy if there is an inadequate response to a PPI. The effect of Helicobacter eradication on healing and recurrence of peptic ulcer: • The effects is dependent upon whether ulceration is gastric or duodenal and whether the patient is taking non-steroidal anti-inflammatory drugs or not. For duodenal ulcers eradication slightly increases healing (additional 5.4% over acid suppression alone) but dramatically decreases recurrence (increases the number of patients ulcer free at 12 months by 52%). For gastric ulcers eradication therapy has no effect on healing but does decrease recurrence (an additional 32% of patients are ulcer free at 12 months compared to acid suppression alone). In patients taking non-steroidal anti-inflammatory drugs eradication therapy has no effect on peptic ulcer healing (gastric or duodenal), but will decrease ulcer recurrence
 continued non-steroidal anti-inflammatory drug use markedly reduces the size of effect that eradication therapy has on reducing ulcer recurrence.

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Endoscopic appearance of ulcers:

• The endoscopic appearances are of two small duodenal ulcers (A) without evidence of recent haemorrhage. There is some co-existent duodenitis.

• The presence of villi identifies this as the duodenum. • The mucosal appearances are not consistent with that of the stomach (absence of rugae, paler squamous epithelium rather than redder columnar epithelium) or the oesophagus (pale pink non-villous squamous epithelium).

Following endoscopic intervention
• immediately post-endoscopy, patients should be commenced on a high dose oral or intravenous proton pump inhibitor, this reduces the risk of rebleeding. • Amoxicillin and clarithromycin may be indicated if there is evidence of Helicobacter pylori infection. This need not be started immediately post-endoscopy but treatment should not be unnecessarily delayed.

Zollinger-Ellison syndrome

Definition • gastrinoma (Zollinger-Ellison syndrome) is a gastrin-secreting neuroendocrine tumor that is most often localized to the duodenum and pancreas.
 Gastrin is released by G cells in the antrum under normal physiological conditions.

Tumor location • Duodenum (~ 70% of cases) Most ulcers are located in the first part of the duodenum. • Pancreas (~ 25% of cases): typically, the head • Ectopic locations (5–15% of cases)
Causes

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• Most gastrinomas occur sporadically. • Around 30% occur as part of MEN type I syndrome

Epidemiology • Sex: ♂ > ♀ (2:1) • Age of onset: 30–50 years
Pathophysiology • Hypergastrinemia → stimulation of parietal cells → gastric acid hypersecretion, which leads to: Peptic ulcer disease Inactivation of pancreatic enzymes → diarrhea, steatorrhea → malabsorption
Features • multiple gastroduodenal ulcers • diarrhoea diarrhea in Zollinger-Ellison syndrome (gastrinoma) is due to malabsorption. • malabsorption Diagnosis • Best initial test: esophagogastroduodenoscopy Important to rule out H. pylori infection and malignant ulcers Typically reveals multiple ulcers and thick gastric folds
 ↓ Gastric pH

• Fasting gastrin levels: the single best screen test fasting gastrin test > 1000 with low PH < 2 is diagnostic
 if level < 1000 and the diagnosis is suspected, then secretin stimulation testing or calcium stimulation testing
 secretin stimulation test
 rise > 200 after 15 minute of dosing is considered positive
 calcium stimulation test
 rise > 395 is considered positive
• Secretin stimulation test (if fasting serum gastrin test is inconclusive) gastrin levels remaining

elevated after administration of secretin.

The presence of multiple, large (> 2 cm) ulcers in atypical locations (e.g., the jejunum) should raise suspicion of gastrinoma.

Treatment • Reduce acid production PPIs (e.g., omeprazole), H2 antagonists (e.g., ranitidine) Octreotide (a somatostatin analog) may be used in refractory cases.
• Non-metastatic disease:
 surgical resection of the gastrinoma is the treatment of choice possibility of cure is up to 25% of patients. • Metastatic disease:
 chemotherapy In approximately 50% of cases, the tumor has already metastasized at the time of diagnosis

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Somatostatin Source Action Regulation Notes • D cells
(pyloric antrum, and duodenum mucosa) • ↓ gastric H+ and pepsinogen secretion • ↓ pancreatic and small intestine fluid secretion • ↓ gallbladder contraction • ↓ insulin and glucagon release • ↓ GH release • delta cells (pancreas) • ventromedial nucleus of the hypothalamus.

• Inhibit TSH secretion.
• Mechanism of action Somatostatin receptor is linked to adenylyl cyclase by Gi protein, which inhibits cAMP production and reduces secretion of hormones.

Somatostatinoma • Annual incidence 1 in 40 million. • Associations: Impaired glucose tolerance (IGT) or diabetes mellitus (95%) Gallstones (68%) Weight loss (25%) (7%) Diarrhoea

• Diagnosis:
 The tumours are often multisecretory ↑↑ Somatostatin, adrenocorticotropic hormone (ACTH) and calcitonin Contrast spiral computed tomography scanning is effective for detecting the primary tumour in only 50% of cases;
 Radiolabeled octreotide or endoscopic ultrasound scanning are often be required. • Treatment:
 surgery is rarely possible due to presence of metastases, hepatic embolisation can be helpful for symptom control.

_Gastric MALT lymphoma Overview • lymphoma of Mucosa-Associated Lymphoid Tissue (MALT)
• (MALT) is typically a low-grade, B-cell neoplasia originating from mucosa-associated lymphoid tissue
• associated with H. pylori infection in 95% of cases • good prognosis • Within the stomach the antrum is most commonly involved Epidemiology • MALT lymphoma
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• Inhibitory hormone • Antigrowth hormone effects (digestion and absorption of substances needed for growth) • Produce vasoconstriction of the splanchnic system. • Somatostatin is treatment for VIPoma and carcinoid tumors • ↑ by H+ • ↓ by vagal stimulation Anaemia (14%) Multiple

endocrine neoplasia type 1

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 7% to 8% of all B-cell lymphomas
 the third most common type of non-Hodgkin's lymphoma the most common type of primary extra-nodal lymphoma and represents up to 50% of primary gastric lymphomas. • Gastric MALT lymphomas
 account for about 30% of all MALT lymphomas,
 median age of 57 years
 no sex predilection.
Features • paraproteinaemia may be present • infiltrate of small-size lymphocytes that destroy gastric glands, configuring the so-called ‘lymphoepithelial lesion’ which is pathognomonic of lymphoma • The common cytogenetic abnormalities demonstrated in MALT lymphomas is t(11;18),
 seen in 30% to 40% of gastric and lung MALT lymphomas This is clinically important, as t(11;18)-positive cases are less likely to respond to H pylori-eradication therapy there is a high incidence of t(11;18) in H pylori-negative gastric MALT lymphoma,
 t(11;18)-positive cases are more likely to present with advanced-stage disease associated with aberrant expression of nuclear BCL10 t(11;18)-positive cases are less likely to transform to aggressive lymphomas, as they are unlikely to develop secondary chromosomal abnormalities.
Treatment • if low grade then 80% respond to H. pylori eradication • low grade localised gastric helicobacter pylori positive : first line antibiotics plus a proton-pump inhibitor (PPI) second line radiotherapy
 Patients are considered to have failed H pylori eradication when: there is no regression at repeat endoscopy 2 months after treatment,
 or when there is lack of complete regression at approximately 18 months after treatment. • low grade localised gastric helicobacter pylori negative: first line radiotherapy • low grade advance gastric (Disease not confined to the stomach) first line chemotherapy
 If H pylori -positive, add eradication therapy. • High grade histological transformation: First line chemotherapy
 MALT lymphoma is defined as a low-grade neoplasm. However, gastric MALT lymphoma can show a component of high-grade transformation.
 This is characterised by an increase in the number of transformed blasts, which can eventually lead to complete effacement of the original MALT lymphoma.

Ref: bestpractice.bmj.com.2017

Gastroparesis

Definition • Delayed gastric emptying in the absence of a mechanical obstruction Causes • Mostly idiopathic but also associated with diabetes mellitus and upper GI surgery • Occurs in 10–20% of diabetics after 10 years.
Mechanism • The major stimulant for gastric motility is “stretch.”

• In patients with longstanding diabetes, there is impaired ability to perceive stretch in the GI tract and impaired motility.
Symptoms
• erratic blood glucose control • chronic nausea, vomiting, epigastric pain, bloating • early satiety, abdominal fullness, constipation. Diagnosis • Gastric-emptying scan
 Gastric emptying scintigraphy demonstrating >10% retention of the radionuclide meal at the end of 4 hours is diagnostic. Management
• Metoclopramide: the first drug of choice
o Action: both a dopamine receptor antagonist and a serotonin receptor agonist.
o Indication: It is better for short-term treatment. Its use in the long-term treatment of gastroparesis is no longer recommended. o Side effects: extrapyramidal
• Domperidone Action: dopamine antagonist with an affinity for the D2 receptor in the brain and peripheral gastrointestinal system.
 Indications: only used for nausea and vomiting and is no longer recommended for the treatment of conditions such as heartburn, bloating, or stomach discomfort. Side effects: associated with a small increased risk of life-threatening cardiac effects. Advantages: It does not cross the blood-brain barrier, so does not cause the neurological adverse effects associated with metoclopramide.
 Contraindications • Contraindicated in patients with hepatic or cardiac disease.
• Should not be administered with other drugs that prolong the QT interval or inhibit CYP3A4 • Erythromycin
 Action: ↑ release of “motilin,” a pro-motility GI hormone. used in the acute care setting if the patient is admitted to hospital.

• Dietary modification (small, frequent meals that are low in fat and contain only soluble fiber), glycemic control and hydration

Type 2 diabetes with erratic blood glucose control or unexplained gastric bloating or vomiting → Think about a diagnosis of gastroparesis.

Gastric cancer

Epidemiology • Sex: ♂ > ♀ (2:1) • Peak incidence: 70 years • Geographical distribution: strong regional differences High incidence in South Korea, China and Japan

Gastroenterology

 Declining incidence in the United States and Europe
• overall incidence is decreasing, but incidence of tumours arising from the cardia is increasing • Adenocarcinoma is the most common gastric cancer (90% of cases). Arises from glandular cells in the stomach. Most commonly located on the lesser curvature Risk factors

• Exogenous risk factors
 Diet: salty, spicy, nitrates, dietary nitrosamines (smoked foods). H. pylori infection: the most common risk factor (> 60%) Smoking Epstein-Barr virus
 Low socioeconomic status
 Obesity • Gastric conditions Pernicious anaemia → Chronic atrophic gastritis → gastric adenocarcinoma. Achlorhydria: decrease in gastric acid production (e.g., due to Ménétrier disease) Gastric ulcers
 Partial gastrectomy Adenomatous gastric polyps Gastroesophageal reflux disease • Hereditary factors Positive family history Blood type A: gAstric cAncer Gastric adenomatous polyps: Hereditary nonpolyposis colorectal cancer • Factors associated with decreased risk of gastric tumours (negative association) Duodenal ulcer NSAID use

Features • Early stages: Often asymptomatic • About half of patients with gastric cancer present with advanced disease at the time of diagnosis. • General signs: Weight loss, chronic iron deficiency anemia • Signs of gastric outlet obstruction: Dysphagia, Abdominal pain, Early satiety, Vomiting • Signs of upper gastrointestinal bleeding: Hematemesis, Melena

• Signs of metastatic disease Hepatomegaly, Ascites: liver is the most common site of metastasis. Left supraclavicular adenopathy (Virchow node)
 Palpable umbilical nodule (Sister Mary Joseph node)
 Mucin-secreting “signet-ring” cells in the ovaries are diagnostic of Krukenberg tumors, which are indicative of stomach adenocarcinoma metastasis. • Paraneoplastic syndromes Leser-Trélat sign (: (multiple seborrheic keratoses, often with an inflammatory base.) Malignant acanthosis nigricans

Always rule out malignancy in patients with acanthosis nigricans.

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Types of gastric adenocarcinoma

• Intestinal type of gastric adenocarcinoma the most common type of gastric adenocarcinoma.
 presents as a large, irregular ulcer with heaped up margins, typically at the lesser curvature of the antrum. associated with Helicobacter pylori, chronic gastritis, atrophy, and intestinal metaplasia

• Diffuse gastric adenocarcinoma
 characterized by thickening and rigidity of the gastric wall.
 Infiltrate the submucosa, (Scirrhous infiltration of the submucosa) so that mucosal sampling may not show neoplastic cells.
 associated with a poor prognosis compared with the intestinal type Unlike the intestinal type of gastric adenocarcinoma, it is more common in women and individuals less than 50 years old. associated with H. pylori infection, but NOT with atrophy and intestinal metaplasia associated with signet ring cells and linitis plastica.
 Linitis plastica is a particularly aggressive form of diffuse adenocarcinoma. It is also known as

"leather bottle stomach" because the stomach is diffusely thickened, with a small lumen that cannot expand, leading to the symptom of early satiety. This thickening can be seen on the CT image.

Histology • Signet ring cells may be seen in gastric cancer.
 They contain a large vacuole of mucin which displaces the nucleus to one side.
 Higher numbers of signet ring cells are associated with a worse prognosis

Diagnosis
• Endoscopy with biopsy: (best initial and confirmatory test) • Staging: CT or endoscopic ultrasound - endoscopic ultrasound has recently been shown to be superior to CT

Treatment • Early-stage disease → surgery alone (Total or sub-total Gastrectomy) • Locally advanced disease → surgery followed by postoperative chemoradiation, or chemotherapy before and after surgery. • Metastatic disease → chemotherapy, immunotherapy, or chemoradiation and supportive care measures. • Trastuzumab is indicated for HER2-positive gastric adenocarcinomas.

Trastuzumab is indicated for HER2-positive gastric adenocarcinomas.

(TRUSTuzumab; HER2; Gastric cancer; Breast cancer)

Post gastrectomy complications • Malabsorption: Lack of chyme stimulation → ↓ pancreatic enzyme levels → protein and carbohydrate maldigestion → fat-soluble vitamin deficiency • Loss of parietal cells → ↓/absent intrinsic factor production → vitamin B12 deficiency → pernicious anemia

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• Loss of parietal cells → ↓ gastric acid → ↓ iron absorption → iron deficiency anemia (low pH environment is necessary for the reduction of Fe3+ (ferric iron) to Fe2+ (ferrous iron) the absorbable form of iron). • Small intestinal bacterial overgrowth • Dumping syndrome
 Early dumping (Occur hours after meal ingestion): rapid emptying of undiluted hyperosmolar chyme into the small intestine → fluid shift to the intestinal lumen → small bowel distention → vagal stimulation → increased intestinal motility (nausea, vomiting, diarrhoea, and cramps) + Vasomotor symptoms such as sweating, flushing, and palpitations. Late dumping (occur hours after meal ingestion): rapid emptying of glucosecontaining chyme into the small intestine → quick reabsorption of glucose → hyperglycaemia → excessive release of insulin → hypoglycaemia and release of catecholamines → signs of hypoglycaemia (e.g., hunger, tremor, light-headedness) Prognosis • At diagnosis, 60% of cancers have already reached an advanced stage that does not allow for curative treatment. • 5-year survival
 confined to the mucosa and submucosa (˃ 90%) extended beyond the submucosa (˂10%).

Gastrointestinal stromal tumour (GIST) • common type of sarcoma; it develops in the gastrointestinal (GI) tract

• occur most often in adults over the age of 50 years
• Location of GISTs:
 most commonly involve the stomach (60%),
 jejunum and ileum (30%),
 duodenum (4%–5%), and
 colorectal (< 5%). • Tumours in the small bowel and rectum appear to be more aggressive than those occurring in the stomach.
• the cell of origin of gastric GISTs Interstitial cells of Cajal within Auerbach's plexus the interstitial cells of Cajal act as pacemaker cells of the GIT, with regulation of peristalsis in the adult intestine
• Approximately 80%–95% of GISTs harbor an activating mutation in the KIT gene about 80% of KIT-negative GISTs have an activating mutation in the PDGFRA gene. a mutation in PDGFRA may make the tumour resistant to the standard drugs to treat GIST. tumours with a PDGFRA mutation are usually less aggressive than the more common ones with KIT mutation. • 50% are present with metastatic disease, (commonly liver metastases),
• Features Mostly asymptomatic. Tumor induce GI bleed and anemia Other symptoms secondry to mass effects: Abdominal discomfort, early satiety, palpable abdominal mass Bowel obstruction or perforation Dysphagia • Diagnosis:
 Gold standard test is endoscopy with biopsy Histopathology: Spindle cell in 70 to 80%, epitheliods cells in 20 to 30

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 CT and endoscopic ultrasound allow tumour staging to plan further management. Immunohistochemical Stainning Up to 95% of GISTs are positive for KIT expression (CD117)
 60%–70% are positive for CD34 expression. • Management all GISTs ≥ 2 cm surgery Surgery is usually the first treatment method used for GIST. If the tumour is too large to be removed at the time of diagnosis, it may be treated initially with imatinib. If sufficient shrinkage has occurred after 6-12 months, it may be operated . incidentally encountered GISTs < 2 cm watchful waiting and surveillance for such very small GISTs might be reasonable. for patients with KIT-positive unresectable and/or metastatic GIST Medical Management:
 first line Imatinib mesylate is an oral adenosine triphosphate (ATP)– competitive TKI that selectively inhibits the activity of KIT, PDGFRA.
 It is effective in 80% of patients and on average will control the disease for about two years. imatinib may be used as an adjuvant therapy after surgery to reduces the risk of the cancer returning second-line In case of imitanib resistance: patients can be switched directly from low-dose imatinib (400 mg/day) to another TKI, such as the only approved second-line therapy, sunitinib. 3rd line Regorafenib (if imatinib and sunitinib are not effective or not tolerated)

Menetrier's disease • A rare condition associated with giant gastric folds, predominantly in the fundus and body of the stomach.
• Histologically there is hyperplasia of the gastric pits, gland atrophy and an increase in overall mucosal thickness.
• Hypochlorhydria is usually present. • Patients often complain of epigastric pain • protein loss

from the gastric mucosa can result in mild hypoalbuminaemia.
• some patients improve spontaneously,whereas in others this can be a premalignant state. • Antisecretory drugs such as proton-pump inhibitors can be tried for symptom relief.

Bowel conditions Dyspepsia Causes of dyspepsia
• Gastro-oesophageal reflux disease (GORD) (15 - 25%) • Gastric and duodenal ulcers (15 - 25%) and • Stomach cancer (2%). • The remaining 60% are classified as non-ulcer dyspepsia (NUD). • Drugs causing dyspepsia NSAIDs (ibuprofen is associated with the lowest risk of peptic ulcer disease) bisphosphonates steroids

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 The following drugs may cause reflux by reducing lower oesophageal sphincter (LOS) pressure calcium channel blockers* nitrates* *calcium channel blockers and nitrates are occasionally used in the management of achalasia, itself a cause of dyspepsia, because of their effect on the LOS. theophyllines

Indications of Urgent referral for an endoscopy (i.e. within 2 weeks). (NICE 2015) • dysphagia • upper abdominal mass consistent with stomach cancer • Any sign of chronic gastrointestinal bleeding • Persistent vomiting • Iron deficiency anaemia, • Suspicious barium meal. • Progressive unintentional weight loss • Patients aged ≥ 55 years who've got weight loss, AND any of the following: upper abdominal pain reflux dyspepsia Non-urgent • Patients with haematemesis • Patients aged >= 55 years who've got: treatment-resistant dyspepsia or upper abdominal pain with low haemoglobin levels or raised platelet count with any of the following: nausea, vomiting, weight loss, reflux, dyspepsia, upper abdominal pain nausea or vomiting with any of the following: weight loss, reflux, dyspepsia, upper abdominal pain Managing patients who do not meet referral criteria ('undiagnosed dyspepsia') • This can be summarised at a step-wise approach

1. Review medications for possible causes of dyspepsia
2. Lifestyle advice
3. Trial of full-dose proton pump inhibitor for one month OR a 'test and treat' approach for H. pylori • lifestyle advice avoid known precipitants: eg: smoking, alcohol, coffee, chocolate, fatty foods and being overweight Raising the head of the bed and having a main meal well before going to bed may help some people. • Testing for H. pylori infection initial diagnosis: NICE recommend using a carbon-13 urea breath test or a stool antigen test, or laboratory-based serology 'where its performance has been locally validated' test of cure: carbon-13 urea breath test • cognitive behavioural therapy and psychotherapy, may reduce dyspeptic symptoms in the short term in individual people. • If H pylori has been excluded and symptoms persist, offer either a low-dose PPI or an H2RA for 4 weeks.

Malabsorption Features • Malabsorption is characterised by diarrhoea, steatorrhoea and weight loss. • The presence of anaemia with low albumin raises the possibility of malabsorption Causes may be broadly divided into:

1. intestinal causes (e.g. villous atrophy), coeliac disease Crohn's disease tropical sprue Whipple's disease Giardiasis brush border enzyme deficiencies (e.g. lactase insufficiency)
2. pancreatic causes (deficiency of pancreatic enzyme production or secretion) chronic pancreatitis cystic fibrosis pancreatic cancer
3. biliary causes (deficiency of bile-salts needed for emulsification of fats) biliary obstruction primary biliary cirrhosis
4. Other causes bacterial overgrowth (e.g. systemic sclerosis, diverticulae, blind loop) lymphoma short bowel syndrome
   Does not develop unless more than two thirds of the small intestine have been removed. features include: Abdominal pain Diarrhea and steatorrhea
   Fluid depletion Weight loss and malnutrition Fatigue complications caused by malabsorption of vitamins and minerals Hyperoxaluria occurs both in patients with an ileal resection and in patients with a short bowel who have had a distal small bowel resection (for example, Crohn's disease, infarcted bowel). What is the most effective advice in preventing further renal calculi? Dietary exclusion of chocolate, tea, rhubarb and spinach
   D-xylose test • D-xylose is a monosaccharide which is absorbed through the small intestines and excreted through the kidneys.
   • D-xylose test is helpful in differentiating between structural and functional causes of malabsorption.
   structural (e.g. Celiac disease, Crohn disease) or functional (e.g. pancreatic insufficiency) • An abnormally low excretion of D-xylose is indicative of a structural pathology.
   • This test distinguishes between malabsorption due to small-intestinal diseases and malabsorption due to pancreatic exocrine insufficiency.
   • A 5-hour urinary excretion of 5 g or greater is normal following the oral administration of 25 g of D-xylose to a well-hydrated subject. • Decreased xylose absorption and excretion are found:
   In patients with damage to the proximal small intestine

 When there is bacterial overgrowth in the small intestine (the bacteria catabolise the xylose) • Patients with pancreatic steatorrhoea (chronic pancreatitis) usually have normal xylose absorption. • Abnormal results might be encountered in renal failure, in the elderly and in patients with ascites due to an excretion defect rather than malabsorption. Diarrhoea (NICE 2012) • Diarrhoea is defined as the abnormal passage of loose or liquid stools more than 3 times daily or a volume of stool greater than 200 g/day.

• Diarrhoea is considered to be chronic if it persists for more than 4 weeks.

Jejunal villous atrophy

Causes • coeliac disease • tropical sprue • hypogammaglobulinaemia • gastrointestinal lymphoma • Whipple's disease • cow's milk intolerance

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Coeliac disease

• Caused by sensitivity to the protein gluten.
• due to T cell mediated hypersensitivity reaction • Mechanism: repeated protein gluten exposure villous atrophy malabsorption. • Conditions associated with coeliac disease include dermatitis herpetiformis (a vesicular, pruritic skin eruption) and autoimmune disorders (type 1 diabetes mellitus and autoimmune hepatitis). • It is strongly associated with HLA-DQ2 (95% of patients) and HLA-B8 (80%) as well as HLA-DR3 and HLA-DR7 • The prevalence of coeliac disease in Europe between 1:100 and 1:300. • It presents at any age but in adults the commonest age of presentation is 20s and 30s. • Women are slightly more commonly affected. • The action of tissue transglutaminase on alpha-gliadin generates epitopes to CD4+ Tlymphocytes, which provoke an inflammatory response in the intestinal wall.

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In 2009 NICE suggest that the following patients should be screened for coeliac disease:

Signs and symptoms Conditions • Chronic or intermittent diarrhoea • Failure to thrive or faltering growth (in children) • Persistent or unexplained gastrointestinal symptoms including nausea and vomiting • Prolonged fatigue ('tired all the time') • Recurrent abdominal pain, cramping or distension • Sudden or unexpected weight loss • Unexplained iron-deficiency anaemia, or other unspecified anaemia • Autoimmune thyroid disease • Dermatitis herpetiformis • Irritable bowel syndrome • Type 1 diabetes • First-degree relatives (parents, siblings or children) with coeliac disease

Associated conditions: • Insulin-dependent diabetes mellitus,
• hypothyroidism,
• chronic liver disease and
• fibrosing alveolitis

Investigations

Diagnosis
• Diagnosis is made by a combination of immunology and jejunal biopsy. Villous atrophy and immunology normally reverses on a gluten-free diet. • If patients are already taking a gluten-free diet they should be asked, if possible, to reintroduce gluten for at least 6 weeks prior to testing. Immunology • tissue transglutaminase (TTG) antibodies (IgA) are the first-choice Selective IgA

deficiency is more common in patients with coeliac disease.

 For this reason, IgA levels should be checked when serological tests are ordered.
 If the patient has selective IgA deficiency tissue transglutaminase IgG can be measured. Patients normally need to be following a gluten-free diet for at least 6 months before the serology becomes negatives. • endomyseal antibody (IgA) 90% sensitive and almost 100% specific.
 Anti-endomysial antibodies are sensitive and specific, but miss the disease in about 5% of the population who are IgA deficient. • anti-gliadin antibody (IgA or IgG) tests are not recommended by NICE • anti-casein antibodies are also found in some patients Jejunal biopsy • duodenal biopsies are the gold standard for diagnosis: villous atrophy crypt hyperplasia increase in intraepithelial lymphocytes lamina propria infiltration with lymphocytes Appearances may resemble severe tropical sprue

Rectal gluten challenge has been described but is not widely used Subtotal villous atrophy is seen in a number of conditions other than coeliac disease such as: • Severe tropical sprue • Cow's milk/soya sensitivity in children • Gastroenteritis • Whipple's disease • Hypogammaglobulinaemia • Neomycin therapy • Laxative abuse • Norwalk agent. Other investigations • Imaging Which would most likely seen on abdominal radiograph with barium contrast? Decreased jejunal folds, increased ileal folds
 imaging and biopsy of the GI mucosa show a characteristic blunting of jejunal villi. This is often associated with a compensatory" jejunization" of the ileum to enhance nutrient absorption.
• Screen for other related autoimmunities
 In a patient with newly diagnosed celiac disease, it is important to screen for other related autoimmunities as well, e.g. type 1 diabetes mellitus and autoimmune thyroiditis.

Management
• gluten-free diet.
 Gluten containing cereals include: wheat: bread, pasta, pastry barley: beer whisky is made using malted barley. Proteins such as gluten are however removed during the distillation process making it safe to drink for patients with coeliac disease rye oats (some patients with coeliac disease appear able to tolerate oats) Some notable foods which are gluten-free include: Rice Potatoes corn (maize)

follow-up
• Tissue transglutaminase antibodies may be checked to check compliance with a gluten free diet.

Associations and Complications If the patient still symptomatic despite being compliant with a gluten free diet think of T Cell lymphoma

• Enteropathy associated T Cell lymphoma (EATL) is a form of Non-Hodgkin's lymphoma
 coeliac disease increase the risk of developing EATL within the 1st year of diagnosis, however with a strict gluten free diet, the risk returns to that of the general population after this point. • Recurrent mouth ulcers • Hyposplenism (Splenic atrophy): seen in 50% of cases and responds poorly to gluten withdrawal.
• selective Ig A deficiency • Small-bowel ulceration is associated with ulcerating jejunitis, but not colonic or gastric ulcers.

MRCPUK-part-1-January 2016 exam: Why do patients with coeliac disease require regular immunisations?
 Functional hyposplenism

Whipple's disease Whipple's disease: jejunal biopsy shows deposition of macrophages containing Periodic acid-Schiff (PAS) granules

• Whipple's disease is a rare multi-system disorder
• Caused by Tropheryma whippelii, a Gram positive bacterium Epidemiology • more common in those who are HLA-B27 positive
• most common in white males aged 40-50 years • rarely is described in women (M:F ratio 9:1). Pathophysiology • Malabsorption in Whipple disease is caused by macrophages in the small bowel lamina propria compressing the lacteals.

Features • malabsorption: diarrhoea, weight loss • large-joint arthralgia • lymphadenopathy • skin: hyperpigmentation and photosensitivity • pleurisy, pericarditis • neurological symptoms (rare): ophthalmoplegia, dementia, seizures, ataxia, myoclonus, characteristic oculo-masticatory movements Investigation • jejunal biopsy shows deposition of macrophages containing Periodic acid-Schiff (PAS) granules •

•

• presence of T. whippelei DNA in tissue by PCR.

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Gastroenterology

Management • oral co-trimoxazole for a year is thought to have the lowest relapse rate, sometimes preceded by a course of IV penicillin • other option:
 initial two week course of parenteral penicillin and streptomycin; followed by a prolonged course (one year) of tetracycline.

Tropical Sprue
• most common in the Carribbean and the Far-East.
 occurs in tropical regions, predominantly central America and South-Eastern Asia. • characterized by a picture of small intestinal malabsorption and the cause is thought to be

infectious in origin. It is thought that an initial GI infection results in small bowel stasis, opportunistic colonisation by organisms such as coliforms, and then a degree of villous atrophy leading to malabsorption and B12, folate deficiency.
 deficiency in folate contributes to greater mucosal injury. Features • Patients classically have a history of recent travel to a tropical area
• present with indigestion, cramps within 2 or 3 weeks after an acute enteric infection.
• Megaloblastic anemia due to folate or B12 deficiency is a common finding.

Diagnosis:
• Jejunal biopsy reveals: Mild villous atrophy ↑↑ villous crypts Mononuclear cellular infiltrates Enlarged epithelial cells Large nuclei caused by folate and/or vitamin B12 deficiency. • barium swallow may show thickening of mucosal folds Treatment: • The main treatment for tropical sprue is broad-spectrum antibiotics (i.e., tetracycline) and vitamin supplementation (i.e., folic acid, vitamin B12).
 Tetracyclines 250mg qds up to 6 months Ampicillin may be used as an alternative in patients who are intolerant of tetracyclines. Folate and B12 deficiencies should also be corrected • Complete recovery is possible with appropriate therapy.

Irritable bowel syndrome (IBS)

Pathophysiology • Studies looking at dietary restriction followed by reintroduction suggest food intolerance in 30-60% of patients with IBS. • increased intestinal contractile and electrical activity with increased sensitivity to visceral stimulation. • Proliferation of intestinal mast cells is a proposed mechanism by which food and stress may trigger symptoms.

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Feature • features supporting a diagnosis of IBS include: A long history with a relapsing and remitting course Exacerbations triggered by life events Symptoms aggravated by eating, and Coexistence of anxiety and depression. • features which suggest organic disease rather than IBS include: Fever Onset of symptoms in old age Progressive deterioration Weight loss Rectal bleeding (not due to fissures or haemorrhoids) Steatorrhoea, and Dehydration.

Diagnosis (NICE 2008) • The diagnosis of IBS should be considered if the patient has had the following for at least 6 months:

1. abdominal pain, and/or
2. bloating, and/or
3. change in bowel habit • A positive diagnosis of IBS should be made if the patient has abdominal pain relieved by defecation or associated with altered bowel frequency stool form, in addition to 2 of the following 4 symptoms:
4. altered stool passage (straining, urgency, incomplete evacuation)
5. abdominal bloating (more common in women than men), distension, tension or hardness
6. symptoms made worse by eating
7. passage of mucus

• Features such as lethargy, nausea, backache and bladder symptoms may also support the diagnosis • Red flag features should be enquired about:

1. rectal bleeding
2. unexplained/unintentional weight loss
3. family history of bowel or ovarian cancer
4. onset after 60 years of age • Also on clinical examination the other 'red flag' indicators are: Anaemia Abdominal mass Rectal mass, and Inflammatory markers for inflammatory bowel disease. • Suggested primary care investigations are: full blood count ESR/CRP coeliac disease screen (tissue transglutaminase antibodies) Management (NICE 2015).

First-line pharmacological treatment - according to predominant symptom • pain: antispasmodic agents Pinaverium is used to reduce the pain duration associated with (IBS).

• diarrhoea: loperamide is first-line • constipation: laxatives but avoid lactulose
• For patients with constipation who are not responding to conventional laxatives linaclotide may be considered, if: optimal or maximum tolerated doses of previous laxatives from different classes have not helped and they have had constipation for at least 12 months Second-line pharmacological treatment • low-dose tricyclic antidepressants (e.g. amitriptyline 5-10 mg) are used in preference to selective serotonin reuptake inhibitors Other management options • psychological interventions - if symptoms do not respond to pharmacological treatments after 12 months and who develop a continuing symptom profile (refractory IBS), consider referring for cognitive behavioural therapy, hypnotherapy or psychological therapy • complementary and alternative medicines: 'do not encourage use of acupuncture or reflexology for the treatment of IBS' General dietary advice • have regular meals and take time to eat • avoid missing meals or leaving long gaps between eating • drink at least 8 cups of fluid per day, especially water or other non-caffeinated drinks such as herbal teas • restrict tea and coffee to 3 cups per day • reduce intake of alcohol and fizzy drinks • consider limiting intake of high-fibre food (for example, whole meal or high-fibre flour and breads, cereals high in bran, and whole grains such as brown rice) • reduce intake of 'resistant starch' often found in processed foods • limit fresh fruit to 3 portions per day • for diarrhoea, avoid sorbitol • for wind and bloating consider increasing intake of oats (for example, oat-based breakfast cereal or porridge) and linseeds (up to one tablespoon per day).
Fibre
• There are two main types of fibre - soluble fibre (which dissolves in water) and insoluble fibre. • It is soluble fibre rather than insoluble fibre that seems to help ease symptoms in some cases. A diet high in soluble fibre is often prescribed for the treatment of IBS Dietary sources of soluble fibre include oats, ispaghula (psyllium), nuts and seeds, some fruit and vegetables and pectins. A fibre supplement called ispaghula powder is also available from pharmacies and health food shops. This seems to be the most beneficial type of supplement. • Insoluble fibre is chiefly found in corn (maize) bran, wheat bran and some fruit and vegetables. In particular, avoid bran as a fibre

supplement.

Malnutrition • Pathophysiology Food intolerance (in 30-60% of patients with (IBS).) increased intestinal contractile and electrical activity with increased sensitivity to visceral stimulation. Proliferation of intestinal mast cells is a proposed mechanism by which food and stress may trigger symptoms. • definition: NICE define malnutrition as the following:

1. a Body Mass Index (BMI) of less than 18.5; or

2. unintentional weight loss greater than 10% within the last 3-6 months; or
3. a BMI of less than 20 and unintentional weight loss greater than 5% within the last 36 months • Around 10% of patients aged over 65 years are malnourished, the vast majority of those living independently, i.e. not in hospital or care/nursing homes. • Screening for malnutrition if mostly done using MUST (Malnutrition Universal Screen Tool).

 it should be done on admission to care/nursing homes and hospital, or if there is concern. For example an elderly, thin patient with pressure sores (The Waterlow score is used to estimate the risk of a patient developing a pressure sore) it takes into account BMI, recent weight change and the presence of acute disease categorises patients into low, medium and high risk • Management of malnutrition is difficult. NICE recommend the following points:

 dietician support if the patient is high-risk a 'food-first' approach with clear instructions (e.g. 'add full-fat cream to mashed potato'), rather than just prescribing oral nutritional supplements (ONS) such as Ensure if ONS are used they should be taken between meals, rather than instead of meals

Waterlow score is used to estimate the risk of a patient developing a pressure sore, this includes an assessment of malnutrition as one of it's components

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Lactose intolerance
• Lactase acts on lactose to generate glucose and galactose. • more common in Asian, and East Asian races. South-east Asian people, like the Vietnamese, Thais, and Chinese, have a very high prevalence of lactase deficiency. • Any GI infection may precipitate the diagnosis of lactose intolerance, as gut flora may be altered by large bowel bacterial or viral load, as well as the treatment of infection. • A change from an Eastern to a Western high lactose diet may also reveal lactose intolerance. • Many patients labelled as having IBS may suffer from undiagnosed lactose intolerance
• many medications use lactose as a binding and stabilising agent. • Diagnosed with a DNA assay of the lactase gene along with a hydrogen breath test.
• Treatment of lactose intolerance is with careful replacement of lactase.

Functional constipation

• The Rome III criteria for functional constipation is as follows (it must include two or more of the following): straining during at least 25% of defecations lumpy or hard stools in at least 25% of defecations sensation of incomplete evacuation for at least 25% of defecations sensation of anorectal obstruction/blockage for at least 25% of defecations manual manoeuvres to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor) fewer than three defecations per week loose stools are rarely present without the use of laxatives, and insufficient criteria for irritable bowel syndrome. • These criteria must be fulfilled for the last three months with symptom onset at least six months prior to diagnosis.