

Objectives

- Describe the common clinical presentations of common gastrointestinal diseases
- Understand the pathophysiology behind selected common non-neoplastic conditions affecting the gastrointestinal tract (GIT)
- Describe the pathogenesis and pathology of tumours of the stomach and gastrointestinal tract, including selected associated cancer syndromes

Outline

I. **Anatomy, Physiology and Congenital Conditions of the GIT**

- a. **Normal Anatomy and Function**
- b. **Manifestations of GI diseases**
- c. **Congenital anomalies:** *Meckel diverticulum, pyloric stenosis, Hirschsprung disease etc.*

II. **Oesophagus**

- a. **Obstruction:** *Mechanical vs Functional*
- b. **Causes of Bleeding:** *Lacerations / perforation and Varices*
- c. **Oesophagitis:** *Reflux oesophagitis (GERD), Eosinophilic oesophagitis (EoE) etc.*
- d. **Barrett oesophagus**
- e. **Tumours:** *Adenocarcinoma, Squamous cell carcinoma*

III. **Stomach**

- a. **Gastropathy, Acute gastritis and Chronic gastritis:** *Helicobacter pylori, Autoimmune etc.*
- b. **Peptic ulcer disease (PUD)**
- c. **Other causes of gastric bleeding:** *Stress-related and non-stress related*
- d. **Miscellaneous non-neoplastic conditions:** *Gastritis cystica, hypertrophic gastropathies*
- e. **Dysplasia**
- f. **Polyyps:** *Inflammatory/hyperplastic, fundic gland polyyps, adenomas*
- g. **Tumours:** *Adenocarcinoma, lymphoma, neuroendocrine tumour (NET), gastrointestinal stromal tumour (GIST)*

IV. **Small intestine and colon**

- a. **Intestinal obstruction (IO):** *Hernia, adhesions, volvulus, intussusception*
- b. **Ischaemic bowel disease**
- c. **Angiodysplasia**
- d. **Malabsorption and Diarrhoea:** *Cystic fibrosis, celiac disease etc.*
- e. **Infectious enterocolitis**
- f. **Irritable bowel syndrome (IBS)**
- g. **Inflammatory bowel disease (IBD):** *Crohn disease and Ulcerative colitis*
- h. **Other forms of colitis:** *Diversion colitis, microscopic colitis (lymphocytic, collagenous), Graft vs host disease*
- i. **Diverticular disease**
- j. **Polyyps:** *Non-neoplastic vs neoplastic*
- k. **Colorectal cancer:** *Polyposis vs non-polyposis syndromes, and colorectal adenocarcinoma*

- V. **Anal canal**
 - a. Haemorrhoids
 - b. Tumours
- VI. **Vermiform appendix**
 - a. Acute appendicitis
 - b. Tumours
- VII. **Peritoneal cavity**
 - a. Peritonitis
 - b. Tumours

References

Kumar V, Abbas A, Aster J. *Robbins & Cotran Pathologic Basis of Disease*. 9th ed.
WHO Classification of Tumours Editorial Board. Digestive system tumours. Lyon (France): International Agency for Research on Cancer; 2019. (WHO classification of tumours series, 5th ed.; vol1).

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Note: Pathweb Study Notes are based on the key topics covered in the lectures in the Yong Loo Lin School of Medicine, as well as additional topics covered in major texts. For more comprehensive discussion on specific pathology topics, readers are advised to refer to the recommended texts in your respective courses.

I. ANATOMY, PHYSIOLOGY AND CONGENITAL CONDITIONS OF THE GIT**Normal anatomy and function**

- Hollow tube extending from oral cavity to anus, with regional variations in structure and function
- Important functions: Motility, secretion, digestion, absorption and excretion

Manifestations of GI diseases

GI diseases may be

- (i) Limited to GIT e.g. peptic ulcer
- (ii) Manifestation of systemic disorder e.g. CMV infection
- (iii) Presents as a systemic disorder but resulting from GI problem e.g. Iron deficiency anaemia from bleeding PUD, vitamin deficiencies due to malabsorption

Cardinal signs and symptoms: Abdominal / chest pain, altered ingestion of food (nausea, vomiting, dysphagia, anorexia), altered bowel movements (diarrhoea or constipation), GI bleeding

Complications: *Acute* – dehydration, sepsis, bleeding, perforation. *Chronic:* Malabsorption (malnutrition, deficiency states), obstruction

Congenital anomalies

- Depends on the nature and timing of the insult during gestation
- Presence of congenital GI anomalies should prompt evaluation of other organs as many organs develop simultaneously during embryogenesis

Atresia, fistulae and duplications

- May occur in any part of the GIT
- *Agenesis* = absence; *atresia* = incomplete development (often resulting in a thin non-canalised cord); *stenosis* = developmental or acquired luminal narrowing due to thickening of the wall. Causes complete / partial mechanical obstruction requiring surgical repair
 - **Oesophageal atresia:** may be associated with a *fistula* connecting the oesophagus to the tracheobronchial tree (tracheo-oesophageal fistula); fistula may also be present without atresia. Results in aspiration, pneumonia, fluid and electrolyte imbalances
 - **Intestinal atresia:** frequently duodenal, or imperforate anus (most common)

Diaphragmatic hernia, omphalocele and gastroschisis

- *Diaphragmatic hernia* = when incomplete formation of the diaphragm allows herniation of the abdominal viscera into the thoracic cavity. If severe, may result in pulmonary hypoplasia
 - **Hiatus hernia** = Due to separation of diaphragmatic crura and widening of space between muscular crura and esophageal wall. Can be congenital or acquired. Associated with reflux oesophagitis and may be a cause of lower oesophageal sphincter incompetence; may be

- complicated by ulceration, bleeding, perforation, strangulation (paraoesophageal hernia), increased risk of oesophageal and gastric adenocarcinoma
- *Omphalocele* = incomplete closure of abdominal musculature, with herniation of the abdominal viscera into a ventral membranous sac. Due to failure of midgut to return to abdomen during midgut rotation. 40% of infants have other associated birth defects (especially heart and renal anomalies)
 - *Gastroschisis* = similar to omphalocele except it involves all layers of the abdominal wall from peritoneum to skin and therefore has no covering sac. Due to defective ingrowth of mesoderm, impaired midline fusion or inappropriate apoptosis. 10-15% may have associated intestinal atresia, but associated anomalies are otherwise rare.

Ectopia

- *Ectopia* = normally formed tissues in an abnormal site ('developmental rests'). Common in GIT e.g. ectopic gastric mucosa in upper oesophagus ('inlet patch') or small bowel/colon, ectopic pancreatic tissue in oesophagus / stomach. Can cause inflammation and scarring with occult bleeding and/or pain

Meckel diverticulum

- *True diverticulum* = blind outpouching of the GIT that communicates with the lumen and includes all three layers of the bowel wall
- *Acquired diverticulum* = lacks or has an attenuated muscularis propria e.g. in sigmoid colon
- Meckel diverticulum is the most common true diverticulum as a result of failed involution of the vitelline duct (connects lumen of developing gut on the antimesenteric side to yolk sac). Often contains ectopic gastric tissue which may result in occult bleeding
- 'Rule of '2's' = occurs in 2% of population, within 2 feet (60 cm) of ileocaecal valve, 2 inches (5 cm) long, twice as common in males and most often symptomatic by age 2 (although only 4% are ever symptomatic)

Pyloric stenosis

- **Congenital vs acquired** (e.g. antral gastritis / peptic ulcers at pylorus, carcinomas of distal stomach or pancreas)
- **Congenital hypertrophic pyloric stenosis** is 3-5x more common in males and has strong but multifactorial pattern of inheritance and genetic basis
- Hyperplasia of the pyloric muscularis propria +/- oedema and inflammation results in gastric outlet obstruction, usually presenting between 3-6th wks of life as projectile non-bilious vomiting after feeding. Surgical splitting of the muscularis (myotomy) is curative

Hirschsprung disease (congenital aganglionic megacolon)

- 1 in 5000 live births; 10% of all cases occur in Down syndrome
- Absence of neural crest derived ganglion cells (both Meissner submucosal and Auerbach myenteric plexus) in the distal colon due to (1) premature arrest of normal migration of neural crest cells from

caecum to rectum, or (2) premature death of ganglion cells. This results in absent peristalsis and functional obstruction, with dilatation of the proximal unaffected bowel segment

- Presents with failure to pass meconium in the immediate postnatal period, followed by constipation, abdominal distension and bilious vomiting, which may be complicated by enterocolitis, fluid and electrolyte imbalances, perforation and peritonitis. Treatment: surgical resection

II. OESOPHAGUS

- Extends from epiglottis in pharynx to gastro-oesophageal junction
- Clinical presentations: Dysphagia, haemetemesis, odynophagia (painful swallowing), heartburn
- **Non-neoplastic conditions:** congenital anomalies, obstruction, lacerations/perforation, varices, oesophagitis, Barrett oesophagus
- **Tumours:** most commonly adenocarcinoma and squamous cell carcinoma

Obstruction

Structural (mechanical) vs **functional** (dysmotility i.e. disruption of the coordinated waves of peristaltic contractions following swallowing)

- **Mechanical obstruction:** stenosis / strictures due to inflammation and scarring (GERD, radiation, caustic injury), mucosal webs or rings, cancer
- **Functional: Achalasia** = triad of (1) incomplete lower oesophageal sphincter (LES) relaxation, (2) increased LES tone and (3) aperistalsis of the oesophagus.
 - **Primary achalasia** = due to distal oesophageal inhibitory neuronal (ganglion cell) degeneration. Cause is unknown
 - **Secondary achalasia** = e.g. Chagas disease where *Trypanosoma cruzi* infection causes destruction of the myenteric plexus, failure of peristalsis and oesophageal dilatation; diabetic autonomic neuropathy etc.

Lacerations / perforation

- One of the causes of haemetemesis
- **Mallory-Weiss tears** = superficial longitudinal tears near the GEJ, most often associated with severe retching due to acute alcohol intoxication. Thought to be due to failure of the reflex oesophageal musculature relaxation preceding the antiperistaltic contractile wave, causing stretching and tearing of the oesophagus by the refluxed gastric contents. Does not usually require surgical intervention
- **Boerhaave syndrome** = transmural tearing and rupture of the distal oesophagus, also usually associated with vomiting, causing severe mediastinitis. Requires urgent surgical intervention.

Varices

- Tortuous dilated veins primarily within submucosa and lamina propria of distal oesophagus and proximal stomach

- Consequence of **portal hypertension**, which causes the development of porto-systemic collateral channels. Present in nearly 50% of cirrhotic patients, with variceal rupture and bleeding in 25-40% (manifesting as **haematemesis +/- melena**) which is an emergency treated medically or endoscopically. However, 30% or more of patients with variceal haemorrhage still die from hypovolemic shock, hepatic coma etc., and those that survive may have recurrent bleeds with mortality risk. **Surveillance with prophylactic treatment** with beta-blockers to reduce portal blood flow and endoscopic variceal ligation helps mitigate the risk.



Oesophagitis

- **Reflux oesophagitis (gastro-oesophageal reflux disease or GERD):** Most frequent cause of oesophagitis. Reflux of gastric juices +/- duodenal bile results in oesophageal mucosal injury
 - **Pathogenesis:** (1) Transient LES relaxation: mediated by vagal pathways and triggered by gastric distension, stress, swallowing-induced (2) Abrupt increase in intra-abdominal pressure: causes forceful opening of a relatively hypotensive LES e.g. coughing, straining. Stratified squamous epithelium of the oesophagus is resistant to abrasion from foods but sensitive to acid, triggering an inflammatory response.
 - **Risk factors:** alcohol, smoking, obesity, CNS depressants, pregnancy, hiatal hernia, delayed gastric emptying and increased gastric volume
 - **Clinical features:** Most common in individuals above 40, but can occur in infants and children. Usually presents with heartburn, dysphagia, sore throat and acid regurgitation. May be complicated by ulceration, haematemesis, melena, strictures, Barrett oesophagus. Proton-pump inhibitors (PPI) to reduce gastric acidity provides symptomatic relief
 - **Endoscopy:** Erythema +/- erosions, ulceration
 - **Histology:** basal zone hyperplasia, elongation of the lamina propria papillae, intraepithelial eosinophils and neutrophils
- **Eosinophilic oesophagitis:** most common cause of GERD-like symptoms in children living in developed countries. Strongly associated with atopy - food allergy, allergic rhinitis, asthma or modest peripheral eosinophilia. **Histology** = large numbers of intraepithelial eosinophils. **Treatment** = dietary restriction to food allergens and topical / systemic corticosteroids. A subset may respond to PPIs.
- **Chemical:** irritants e.g. alcohol, corrosive acids/alkalis, pill-induced, chemotherapy
- **Radiation:** vascular injury resulting in mucosal damage
- **Infections** (immunocompetent vs immunocompromised): *Herpes simplex virus (HSV)* [punched-out ulcers, epithelial viral nuclear inclusions], *cytomegalovirus (CMV)* [shallower ulcers, stromal nuclear and cytoplasmic inclusions], fungal e.g. *Candidiasis* [adherent gray-white pseudomembranes, fungal hyphae]
- **Graft-vs-host disease:** basal epithelial cell apoptosis without significant acute inflammation
- **Involvement by skin diseases** e.g. bullous pemphigoid

Barrett oesophagus (BE)

- Complication of chronic GERD characterized by columnar / intestinal metaplasia within the oesophageal squamous mucosa.
- **Clinical features:** Rising incidence, ~10% of individuals with symptomatic GERD. White males, 40-60yo. Risk factor for dysplasia (preinvasive change) and oesophageal adenocarcinoma. Presence of dysplasia a/w prolonged symptoms, longer segment length, increased patient age and Caucasian race. Management is controversial, but most currently do periodic endoscopy with biopsy for dysplasia surveillance. Intramucosal or submucosal invasive carcinoma requires treatment.
- Diagnosis requires endoscopy and histology:
- **Endoscopy:** tongues / patches of red velvety mucosa extending upward from the GEJ, alternating with the pale smooth squamous oesophageal mucosa and interfacing distally with the light brown columnar gastric mucosa. Long segment = 3cm or more, short segment = less than 3 cm
- **Histology:** columnar / intestinal metaplasia (requirement of goblet cells depends on UK/US guidelines). Dysplasia is characterized by architectural and cytologic atypia, and can be low or high grade.

Adenocarcinoma

- Most oesophageal adenocarcinomas arise from Barrett oesophagus → usu. distal 1/3 of oesophagus, may involve the gastric cardia
- **Risk factors:** GERD, smoking, radiation, reduced rates of H.pylori infection (because H.pylori causes gastric atrophy which reduces acid secretion and reflux and therefore Barrett oesophagus)
- **Pathogenesis:** Progression from BE to adenocarcinoma occurs over an extended period through the stepwise acquisition of genetic and epigenetic changes. *Early stages:* chromosomal abnormalities, TP53 mutation, downregulation of CDKN2A (p16/INK4a). *Later progression:* amplification of EGFR, ERBB2, MET, cyclin D1 and cyclin E
- **Clinical features:** Caucasian males. Rapid increase in incidence since 1970s. Patients usually present with pain or dysphagia, progressive weight loss, haemetemesis, chest pain or vomiting. Tumour usually has already spread to submucosal lymphatic vessels by the time patients are symptomatic and therefore has poor prognosis due to advanced stage at presentation. Prognosis is much better (5yr survival of 80%) in tumours limited to mucosa or submucosa.
- **Gross:** flat/raised patches, ulceration, diffuse infiltration
- **Histology:** adjacent BE. Gland formation +/- mucin, often intestinal-type or less commonly signet-ring cell morphology.

Squamous cell carcinoma

- 50% in middle third of oesophagus
- **Risk factors:** Alcohol and tobacco use, poverty, caustic oesophageal injury, achalasia, frequent consumption of very hot beverages, diets deficient in fruits or vegetables, nutritional deficiencies, mutagenic compounds e.g. nitrosamines and polycyclic hydrocarbons, HPV infection in high risk areas

- **Pathogenesis:** Molecular pathogenesis incompletely defined, but recurrent abnormalities include SOX2 amplification, cyclin D1 overexpression and loss of function mutations in tumour suppressors TP53, e-cadherin and NOTCH1
- **Clinical features:** M:F = 4:1, older than 45 years old, African-Americans. Usually insidious onset, presenting with dysphagia, odynophagia or obstruction (with subconscious adjustment of diet from solid to liquid foods), prominent weight loss due to impaired nutrition and effects of tumour itself. **Complications:** Tumour ulceration causing haemorrhage, iron deficiency anemia and sepsis; local invasion into surrounding structures e.g. trachea-oesophageal fistula resulting in aspiration of food and pneumonia; aorta-oesophageal fistula causing exsanguination. **Prognosis:** Poor, especially with advanced tumours and LN metastases (which are common - LN drainage = upper 1/3: cervical LN, middle 1/3: mediastinal, paratracheal and tracheobronchial LN, lower 1/3: gastric and celiac LN)
- **Gross:** Small grey-white plaque-like thickenings, growing into tumour masses that may be polypoid / exophytic, protruding and obstructing the lumen. Also may be ulcerative or diffusely infiltrative lesions, causing thickening, rigidity and luminal narrowing. Rich lymphatic network promotes circumferential and longitudinal spread; tumour nodules may present several cm away from the principal mass
- **Histology:** Begins as in-situ lesion (squamous dysplasia → carcinoma in-situ). Most SqCC are well to moderately differentiated.

III. STOMACH

- 4 major anatomic regions: Cardia, fundus, body, antrum.
 - **Cardia and antrum:** mucin-secreting foveolar cells that form small glands. Antral glands also contain endocrine G cells that release gastrin to stimulate luminal acid secretion by parietal cells in the body and fundus
 - **Body and fundus:** acid-secreting parietal cells (also secretes intrinsic factor) and digestive enzymes-secreting chief cells (oxyntic mucosa)
- Normal gastric lumen is extremely acidic (pH close to 1), which contributes to digestion but has potential to damage mucosa
- Clinical presentations: asymptomatic, epigastric pain, nausea, vomiting, haematemesis, melena

Gastropathy and acute gastritis

- **Gastritis** = mucosal inflammation. Acute gastritis = neutrophils present
- **Gastropathy** = gastric dysfunction or injury with rare or absent inflammatory cells. Causes: NSAIDs, alcohol, bile, stress-induced, portal hypertension.
 - **Hypertrophic gastropathy:** specific group of diseases including Menetrier disease and Zollinger-Ellison syndrome
- **Causes:** Chemical e.g. alcohol, bile reflux (post-gastrectomy), corrosives, chemotherapy; radiation therapy; NSAIDs; corticosteroids. Contributory factors: Smoking, elderly age (?due to reduced mucin and bicarbonate secretion), high altitudes (decreased oxygen)

- **Pathogenesis:** Disruption of the normal protective mechanisms in the stomach –
 - (i) **Mucus barrier:** mucin secretion by surface foveolar cells forms a thin layer of mucus and phospholipids that prevents large food particles from directly touching the epithelium
 - (ii) **Bicarbonate secretion:** the mucus layer has a neutral pH as a result of bicarbonate ion secretion by surface epithelial cells
 - (iii) **Epithelial barrier:** the gastric epithelial cells beneath the mucus layer has intercellular tight junctions, forming a physical barrier that limits back-diffusion of acid and leakage of other luminal materials, including pepsin, into the lamina propria. The epithelial layer is maintained by complete replacement of the surface foveolar cells every 3 to 7 days
 - (iv) **Rich mucosal blood flow:** delivers bicarbonate, oxygen and nutrients to epithelial cells while washing away acid that has back-diffused into the lamina propria. In acid-secreting parts of the stomach, a capillary 'alkaline tide' is generated as parietal cells secrete hydrochloride acid into the gastric lumen and bicarbonate into the vessels

NSAIDs: inhibit cyclooxygenase (COX)-dependent synthesis of prostaglandins E₂ and I₂, which stimulate nearly all of the above defense mechanisms while reducing acid secretion. Both COX1 and 2 isoenzymes contribute to mucosal protection, so even selective COX2 inhibitors e.g. celecoxib can result in gastropathy or gastritis

Uremic patients and urease-secreting H.pylori: inhibition of gastric bicarbonate transporters by ammonium ions

Chemicals/alcohol/chemoradiotherapy: Direct mucosal damage to both epithelial and stromal cells. Chemotherapy agents that inhibit DNA synthesis or the mitotic apparatus also cause generalized mucosal damage by insufficient epithelial renewal

- **Clinical presentation:** depends on etiology e.g. NSAID-induced gastropathy may be asymptomatic, or persistent epigastric pain that responds to antacids or PPIs, while pain associated with bile reflux is refractory to such therapies and may be accompanied by occasional bilious vomiting
- **Histology:** foveolar hyperplasia, lamina propria oedema and vascular congestion. Neutrophils seen in **acute gastritis** (vs 'gastropathy'). **Acute erosive haemorrhagic gastritis** = erosions (superficial mucosal defect due to loss of epithelium) in more severe mucosal damage +/- haemorrhage. Extensive erosions may progress to **ulcers**

Chronic gastritis

- Chronic mucosal inflammation that can lead to mucosal atrophy and intestinal metaplasia (IM)
- **Causes:** Most common - **Helicobacter pylori infection** (longstanding can result in atrophic, usually multifocal, gastritis). Others - **autoimmune gastritis** (most common cause of diffuse atrophic gastritis), radiation injury, chronic bile reflux, mechanical injury, involvement by systemic diseases e.g. Crohn disease, amyloidosis, graft vs host disease
- **Clinical presentation:** Symptoms usually less severe but more persistent compared to acute gastritis. Nausea, abdominal pain, +/- vomiting. Haematemesis is uncommon.
- **Complications:** **Peptic ulcer disease, mucosal atrophy which is associated with intestinal metaplasia (IM)** and a risk factor to gastric adenocarcinoma (greatest in autoimmune gastritis, possibly because achlorhydia of gastric mucosal atrophy permits overgrowth of bacteria that

produce carcinogenic nitrosamines. IM in chronic H.pylori gastritis may regress after clearance of the organisms)

Helicobacter pylori gastritis

- Spiral-shaped or curved bacilli that causes predominantly **antral** gastritis with normal or increased (local) gastrin production
- **Pathogenesis:** Pattern of H.pylori gastritis is a result of interplay between gastroduodenal mucosal defenses, host inflammatory responses and bacterial virulence factors. There is an inverse relationship between risk of duodenal ulcer and gastric adenocarcinoma depending on the pattern:
 1. *Antral-limited:* Greater risk of **duodenal peptic ulcer** due to the **increased** acid production (due to stimulation of gastrin release by cytokines released or specific products of H.pylori)
 2. *Pangastritis:* Body and fundus progressively involved, resulting in multifocal atrophic gastritis associated with **reduced** parietal cell mass and acid secretion, IM and increased risk of **gastric adenocarcinoma**

Virulence of H.pylori is linked to several factors:

- Flagella: allows the bacteria to be motile in viscous mucus
- Urease: generates ammonia from endogenous urea and thereby elevates local gastric pH and enhances bacterial survival
- Adhesins: enhance bacterial adherence to surface foveolar cells
- Toxins: cytotoxin-associated gene A (CagA) and the associated 20 gene pathogenicity islands that are present in 50% of H.pylori isolates overall but 90% in populations with elevated gastric cancer risk and therefore may be involved in disease progression, partly because CagA expressing strains can effectively colonize the gastric body and cause multifocal atrophic gastritis

Host factors:

- Genetic polymorphisms that lead to increased expression of proinflammatory cytokines tumour necrosis factor (TNF) and interleukin IL-1b or decreased expression of the anti-inflammatory cytokine IL-10 are associated with development of pangastritis, atrophy and gastric cancer.
- Iron deficiency may also be risk factor of H.pylori associated gastric cancer
- **Clinical features:** **Fecal-oral** transmission → higher rates in areas of poverty, household crowding. Infection typically acquired in childhood and persists for life without treatment. Mostly asymptomatic; symptoms usually only in chronic infection. **Complications:** Peptic ulcer, gastric adenocarcinoma, gastric lymphoma. **Treatment:** combination of antibiotics (triple therapy) and proton pump inhibitor. Relapses can occur after incomplete eradication or reinfection, which is common in regions with high endemic colonization rates
- **Endoscopy:** erythematous mucosa +/- coarse nodular appearance
- **Histology:** H.pylori organisms within the superficial mucus overlying the epithelial cells in the surface and neck regions (has tropism for gastric epithelia, not found in areas of IM or duodenal epithelium). Can be demonstrated with special stains

1. *Antral-limited* (usually): +/- cardia → antral biopsies performed for evaluation of H.pylori. Mucosa shows mixed inflammatory infiltrate: neutrophils (activity), plasma cells, lymphocytes (+/- lymphoid aggregates) and macrophages
 2. *Pangastritis* (if long standing): In addition to inflammation, body and fundus show patchy mucosal atrophy (loss of chief and parietal cells → looks like antral mucosa) (vs. diffuse atrophy in autoimmune gastritis), typically associated with IM and increased risk of gastric adenocarcinoma
- **Other diagnostic tests:** (*Non-invasive*) Serologic test for H.pylori antibodies, fecal bacterial detection, urea breath test (based on conversion of urea into ammonia and CO₂ by bacterial urease). (*Invasive*) Gastric biopsy specimens can also be analyzed by rapid urease test, bacterial culture or PCR detection of bacterial DNA

Autoimmune (AI) gastritis (*less than 10% of chronic gastritis*)

- **Body**-predominant gastritis characterized by antibodies to parietal cells and intrinsic factor (IF) (can be detected in serum and gastric secretions), resulting in defective gastric acid secretion (**achlorhydria**), endocrine cell hyperplasia (**hypergastrinemia**), decreased ileal vitamin B12 absorption (leading to deficiency and **pernicious anaemia**) and **reduced serum pepsinogen I secretion** (from chief cells)
- **Pathogenesis: Autoimmune destruction of parietal cells** (which secretes gastric acid and IF) causes:
 - **Absence of acid production (achlorhydria)**, stimulating increased gastrin secretion (hypergastrinemia), hyperplasia of the antral gastrin-producing G cells and hyperplasia of enterochromaffin-like cells in the gastric body (neuroendocrine cell hyperplasia, which can progress to form small multicentric low grade neuroendocrine tumours). Achlorhydria also decreased iron absorption (iron deficiency anaemia)
 - **Lack of intrinsic factor**, disabling ileal vitamin B12 absorption, leading to vitamin B12 deficiency and slow-onset megaloblastic anaemia (pernicious anaemia)

Chief cell destruction also occurs (through general gastric gland destruction during the autoimmune attack on the parietal cells), resulting in reduced serum pepsinogen I concentration

Note: *H.pylori chronic gastritis doesn't have achlorhydria or pernicious anaemia despite gastric atrophy because it is usually patchy / multifocal with residual patches of parietal and chief cells vs diffuse atrophy of AI gastritis*

The principal agent of injury is actually **CD4+ T cells** directed against parietal cell components, including the H⁺, K⁺-ATPase proton pump. Autoantibodies against parietal cell components (including the proton pump) and intrinsic factor are present in 80% of patients with AI gastritis but are NOT thought to be pathogenic - neither secreted IF nor the lumenally oriented proton pump are accessible to the circulating antibodies, and passive transfer of the antibodies does not produce gastritis in experimental animals. Hence they are important mainly for diagnosis only

- **Clinical features:** slow onset disease with variable progression to gastric atrophy over 2-3 decades – median age at diagnosis is 60, and anaemia is only seen in a few patients. Patients may present with symptoms of anaemia or vitamin B12 deficiency (atrophic glossitis, malabsorptive diarrhoea, peripheral neuropathy with numbness or paraesthesias, cerebral dysfunction e.g. memory loss,

personality changes, subacute combined degeneration of the spinal cord). Slightly more F>M; a/w other autoimmune diseases e.g. Hashimoto thyroiditis, but little evidence of linkage to specific HLA alleles so far. **Treatment:** Prevention/treatment of vitamin B12 and iron deficiencies (prevention is important because unlike anaemia, neurologic changes are not reversed by vitamin B12 therapy)

- **Histology: diffuse mucosal atrophy** of the oxyntic glands (chief and parietal cells) within body and fundus +/- intestinal metaplasia, with no/minimal damage to antrum and cardia. Mainly chronic inflammation (lymphocytes, macrophages, plasma cells with lymphoid aggregates) +/- neutrophils, deep in the lamina propria and centered on the gastric glands. Also varying degrees of neuroendocrine cell hyperplasia +/- neuroendocrine tumours

	H.pylori associated gastritis	Autoimmune gastritis
Location	Antrum	Body
Inflammation	Neutrophils, subepithelial plasma cells	Lymphocytes, macrophages, plasma cells +/- neutrophils
Acid production	Increased to slightly decreased	Decreased
Gastrin	Normal to decreased	Increased
Complications	Peptic ulcer, adenocarcinoma, MALT lymphoma	Atrophy, pernicious and iron deficiency anaemia, adenocarcinoma, neuroendocrine tumours

Eosinophilic gastritis

- Tissue damage associated with dense infiltrates of eosinophils in the mucosa and muscularis, usually antral or pyloric region. May be caused by allergic reactions e.g. cow's milk allergy, in association with some immune disorders e.g. systemic sclerosis, parasitic infections and H.pylori infection
- May affect other GI sites, a/w peripheral eosinophilia and raised serum IgE levels

Lymphocytic gastritis

- Idiopathic but 40% associated with celiac disease, suggesting an immune-mediated pathogenesis. Typically affects entire stomach
- F>M, presents with non-specific abdominal symptoms
- Endoscopy: thickened gastric folds covered by small nodules with central aphthous ulceration on endoscopy (varioliform gastritis). Histology: Marked increase in intraepithelial T lymphocytes

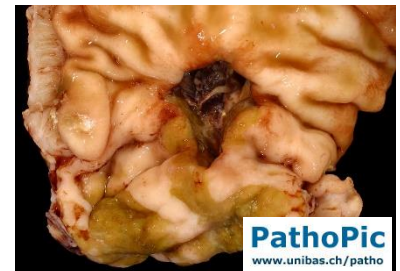
Granulomatous gastritis

- Descriptive term for any gastritis that contains granulomas / aggregates of epithelioid macrophages. E.g. Idiopathic, gastric involvement by Crohn disease, sarcoidosis, infections

Peptic ulcer disease (PUD)

- Chronic mucosal ulceration affecting the duodenum or stomach, usually due to H.pylori infection
 - *Antrum/proximal duodenum (most common location)*: usually due to chronic H.pylori induced antral gastritis, which is associated with **increased** acid secretion and decreased duodenal bicarbonate secretion

- *Body/fundus*: usually due to some *H.pylori* gastritis or AI gastritis, resulting in mucosal atrophy and **lesser** acid secretion. Therefore protects from antral/duodenal ulcers
- *Oesophagus (rare)*: due to GERD or acid secretion by ectopic gastric mucosa (can occur occur in duodenum or Meckel diverticulum)
- **Pathogenesis**: Imbalance between mucosal defenses and damaging factors of chronic gastritis (PUD therefore generally develops on a background of chronic gastritis). Likely host and bacterial factors determine why some people develop only chronic gastritis and others get PUD
- **Clinical features**: Most due to **H.pylori** infection, **NSAIDs** (potentiated by steroids) or cigarette **smoking** (synergizes with *H.pylori* for gastric PUD). Rare causes e.g. Zollinger-Ellison syndrome
Presentation: Epigastric burning or aching pain (can be chronic/recurring, occurring 1-3hrs after meals, worse at night and relieved by alkali or food). With penetrating ulcers, pain may be referred to the back, left upper quadrant or chest, mimicking cardiac chest pain. Nausea/vomiting, bloating/belching, weight loss. May also be symptomatic from complications e.g. iron deficiency anaemia, haemorrhage or perforation.
Complications: **Bleeding** (most frequent - 15-20% of patients; may be life threatening or first presentation); **Perforation** (5%; accounts for 2/3 of ulcer deaths – surgical emergency!); **Obstruction** (2%; mostly in chronic ulcers, secondary to oedema or scarring usually in pyloric channel ulcers +/- duodenal ulcers). Malignant transformation occurs rarely, if ever.
Treatment: *H.pylori* eradication, neutralization of gastric acid (primarily with proton pump inhibitors (PPI)), and withdrawal of offending agents e.g. NSAIDs. Surgery for treatment of bleeding or perforated ulcers (previously, antrectomy and vagotomy to prevent the acid-stimulatory effects mediated by the vagus nerve, but now not necessary with medical treatment)
- **Gross**: Solitary (>80%), round to oval, sharply punched-out defect with a smooth clean ulcer base as a result of peptic digestion of exudate. The mucosal margin may overhang the base slightly, but is usually level with surrounding mucosa vs. heaped up margins characteristic of cancers. (Note: Size and location do not differentiate between benign and malignant ulcers)
- **Histology**: thin surface layer of fibrinopurulent exudate, underlying suppurative necrosis, granulation tissue with mononuclear leukocytes, and a fibrocollagenous scar forming the ulcer base. Vessel walls are thickened and possibly thrombosed within the scarred area – bleeding from these damaged vessels from the ulcer base may cause life-threatening haemorrhage.



Stress-related mucosal disease

- Occurs in patients with severe physiologic stress, usually during the 1st 3 days (*acute*)
 - **Stress ulcers**: shock, sepsis, severe trauma, post-myocardial infarction
 - **Curling ulcers**: severe burns or trauma. Proximal duodenum
 - **Cushing ulcers**: intracranial disease. Duodenum and oesophagus. High incidence of perforation

Healing with complete re-epithelisation occurs within days to several weeks after correction of the underlying condition

- **Pathogenesis:** Local ischaemia from systemic hypotension or stress-induced splanchnic vasoconstriction, upregulation of inducible nitric oxide synthase and increased release of vasoconstrictor endothelin-1. Other contributing factors: systemic acidosis, gastric acid hypersecretion from vagal nuclei stimulation in intracranial injuries
- **Gross:** shallow erosions to deeper ulcers anywhere in stomach, usually multiple, rounded and less than 1 cm in size. Ulcer base frequently stained brown to black by acid digestion of extravasated blood
- **Histology:** erosion/ulcer sharply demarcated with adjacent normal mucosa. No scarring or blood vessel thickening seen in peptic ulcers (which arise in the setting of *chronic* injury).

Non-stress related causes of gastric bleeding

- **Dieulafoy lesion:** submucosal artery that does not branch properly within the wall of the stomach, resulting in a mucosal artery 10x the size of mucosal capillaries. Usually lesser curvature near the GEJ. Erosion of the overlying mucosal epithelium can cause self-limited but copious gastric bleeding. Bleeding often associated with NSAID use and can be recurrent
- **Gastric antral vascular lesion (GAVE):** Mostly idiopathic but can also be associated with cirrhosis and systemic sclerosis. **Endoscopy** - longitudinal stripes of oedematous erythematous mucosa created by ectatic mucosal vessels alternates with less severely injured, paler mucosa ('watermelon stomach'). **Histology** - antrum shows reactive gastropathy with dilated capillaries containing fibrin thrombi

Other miscellaneous non-neoplastic conditions

Gastritis cystica: Exuberant reactive epithelial proliferation associated with entrapment of epithelial-lined cysts within the submucosa (gastritis cystica polyposa) or deeper layers of the gastric wall (gastritis cystica profunda). Mimics invasive adenocarcinoma

Hypertrophic gastropathies: Characterized by giant 'cerebriform' enlargement of the rugal folds due to epithelial hyperplasia without inflammation, linked to excessive growth factor release

- **Menetrier disease:** rare disorder caused by excessive secretion of TGF α characterized by diffuse foveolar hyperplasia of the gastric body and fundus, and hypoproteinaemia due to protein-losing enteropathy. A/w weight loss, diarrhoea. Risk of gastric adenocarcinoma increased in adults. Treatment is supportive
- **Zollinger-Ellison syndrome:** Caused by gastrin-secreting tumours ('gastrinomas') commonly found in small intestine or pancreas. Can be sporadic (75%) or syndromic (MEN1). Gastrinomas cause parietal cell hyperplasia and acid hypersecretion → often present with peptic ulcers. **Histology:** Marked thickening of oxyntic mucosa due to marked increase in parietal cells, hyperplasia of mucous neck cells, mucin hyperproduction and proliferation of endocrine cells within the oxyntic mucosa

(neuroendocrine cell hyperplasia → tumour). **Treatment:** blockade of acid hypersecretion usu. with PPIs, and treatment of the gastrinoma.

Dysplasia

- Preinvasive in-situ lesion with architectural and cytologic atypia
- Often arises in background of chronic gastritis, which exposes the epithelium to inflammation-related free radical damage and proliferative stimuli that lead to the accumulation of genetic alterations over time that result in carcinoma

Polyyps

Develop due to epithelial or stromal cell hyperplasia, inflammation, ectopia or neoplasia.

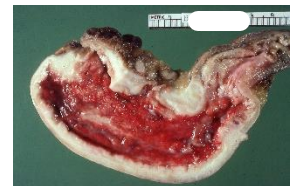
- **Inflammatory and hyperplastic polyyps:** 75% of all gastric polyyps. Reactive lesions, usually in a/w chronic gastritis which initiates the injury that leads to reactive hyperplasia and polyp growth. Risk of dysplasia correlates with polyp size
- **Fundic gland polyyps:** sporadic or in patients with familial adenomatous polyposis (FAP). Increasing incidence with use of PPI therapy, which inhibits acid production, thereby increasing gastrin secretion which stimulates oxyntic gland growth. Sporadic polyyps have no cancer risk, while FAP-associated polyyps may develop dysplasia and cancer
- **Gastric adenoma:** 10% of all gastric polyyps. Frequency increases with age; prevalence varies and parallels incidence of gastric adenocarcinoma. M:F = 3:1. Incidence also increased in FAP patients. Similar to dysplasia, it occurs on a background of chronic gastritis with atrophy and intestinal metaplasia. Significant risk of adenocarcinoma (up to 30% of adenomas; related to size of lesion) → requires more aggressive therapy than colonic adenomas

Gastric adenocarcinoma

- More than 90% of all gastric cancers. Malignant epithelial neoplasm with glandular differentiation - Two main (Lauren) histologic subtypes: **Intestinal-type** and **diffuse-type**
 - **Intestinal-type:** Predominates in high-risk areas (e.g. Japan, East Europe). Precursor lesions include flat dysplasia and adenoma. M:F = 2:1
 - **Diffuse-type:** Incidence is relatively uniform across countries, with no clearly identified precursor lesions. M=F.
- **Risk factors:** Lower socioeconomic status, multifocal mucosal atrophy, intestinal metaplasia. PUD is not a risk factor (although patients with partial gastrectomies for PUD have a slightly higher risk of developing cancer in the residual gastric stump, possibly due to hypochlorhydria, bile reflux and chronic gastritis)
- **Pathogenesis:** Majority are sporadic; familial gastric cancers tend to be diffuse-type.
 - *Diffuse-type:* Loss of expression of cell adhesion protein **E-cadherin** is a key step. This may occur via **loss of function mutations** in the **tumour suppressor gene CDH1** which encodes E-cadherin (germline loss is strongly associated in familial gastric cancer, but loss of function is also seen in ~50% of sporadic diffuse-type tumours). Other mechanisms of decreased E-

cadherin expression in sporadic tumours include hypermethylation and silencing of the *CDH1* promoter. *CDH1* mutations are also common in sporadic and familial breast lobular carcinoma. Individuals with **BRCA2 mutations** are also at increased risk of developing diffuse gastric cancer

- **Intestinal-type:** Strongly associated with mutations that result in **increased signaling via the Wnt pathway**, including loss-of-function mutations in the **adenomatous polyposis coli (APC) tumour suppressor gene** and gain-of-function mutations in the **gene encoding b-catenin**. FAP patients (who carry germline *APC* mutations) thus have increased risk of intestinal-type gastric cancer. Loss of function mutations or silencing of a number of other tumour suppressor genes including those involved in TGF- β signaling, regulation of apoptosis (BAX) and cell cycle control (CDKN2A)
- **TP53 mutations** are also found in the majority of sporadic gastric cancers of both diffuse and intestinal types
- **Chronic inflammation** promotes gastric neoplasia: Genetic variants of proinflammatory and immune response genes, including those that encode IL-1 β , TNF, IL-10, IL-8 and Toll-like receptor 4 (TLR4), are associated with elevated risk of gastric cancer when accompanied by *H.pylori* infection. **Environmental factors** also affect risk
- **Clinical features:** Overall incidence falling due to decrease in intestinal-type gastric carcinoma, paralleling the decrease in *H.pylori* prevalence and decreased consumption of dietary carcinogens (found in preserved foods), although cancer of the gastric cardia is increasing (whose profile is similar to distal oesophageal adenocarcinomas). **Early symptoms are usually non-specific** (e.g. dyspepsia, nausea, dysphagia). Tumours are therefore often diagnosed at late stage with weight loss, anorexia and haemorrhage. **Treatment:** Surgical resection (preferred); if not, chemotherapy, radiotherapy and palliative care. **Prognosis:** depends on depth of tumour invasion (e.g. into adjacent organs), extent of nodal and distant metastases. Favourite sites of metastases: supraclavicular LN (Virchow node), periumbilical LN (Sister Mary Joseph nodule), ovary (Krukenberg tumour), pouch of Douglas (Blumer shelf). Also suggested that diffuse histologic type may have worse prognosis than intestinal type. 5 yr survival rate can exceed 90% in early gastric cancer (i.e. tumour with no deeper than submucosal invasion irrespective of LN mets), but is overall low because of advanced stage at presentation → screening is important
- **Gross:** mostly antrum (lesser curve > greater curve)
 - **Intestinal-type:** usually bulky **exophytic** masses or **ulcers/excavated**
 - **Diffuse-type:** usually **flat/depressed**, widely infiltrative, inducing stromal desmoplasia that thickens and stiffens the gastric wall and causes rugal flattening, imparting a leather bottle appearance ('linitis plastica'), rather than forming a discrete tumour mass
- **Histology:**
 - **Intestinal-type:** glandular structures with apical and luminal mucin
 - **Diffuse / poorly cohesive-type:** discohesive cells that infiltrate singly or in small clusters and do not form glands; may have 'signet-ring cell' appearance (i.e. large intracytoplasmic mucin vacuole that pushes the nucleus to the periphery)



Lymphoma

- Extranodal lymphomas arise commonly in the GI tract, especially the stomach. ~5% of all gastric malignancies are primary lymphomas, most commonly **extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)**. MALT lymphoma can transform into more aggressive tumours that are histologically identical to **diffuse large B-cell lymphoma (DLBCL)**, often in association with additional genetic changes
- **Pathogenesis:** MALToma usually arises at sites of chronic inflammation - H.pylori infection is the most common inducer of MALT lymphoma in the stomach, possibly via NF-KB dysregulation. NF-KB is a transcription factor that promotes B-cell growth and survival. The 3 chromosomal translocations associated with gastric MALT lymphoma t(11;18), t(1;14) and t(14;18) also result in constitutive activation of NF-KB
- **Clinical presentation:** dyspepsia, epigastric pain +/- haematemesis, melena and constitutional symptoms. **Treatment:** H.pylori eradication (results in durable remission with low rates of recurrence in most patients). Radiation/chemotherapy may be required with failure of H.pylori eradication e.g. tumours with translocations (due to constitutive activation of NF-KB), tumours invading to the muscularis propria or beyond, lymph node involvement, or transformation to DLBCL
- **Histology:** dense lymphoid infiltrate in the lamina propria, which infiltrates gastric glands to form lymphoepithelial lesions. Expresses B cell marker CD20, negative for CD5 and CD10.

Well-differentiated Neuroendocrine Tumours (NET)

- Previously known as carcinoid or 'carcinoma-like' tumours as they have a more indolent clinical course than GI carcinomas; more than 40% of GI NET occur in the small intestine
- **Risk factors / associations:** Neuroendocrine cell hyperplasia, autoimmune chronic atrophic gastritis, MEN1 and Zollinger-Ellison syndrome. PPI therapy may be associated with NE cell hyperplasia but the risk of progression to a NET is extremely low
- **Clinical presentation:** Asymptomatic or symptomatic depending on the hormones produced e.g. gastrin-secreting tumours may cause **Zollinger-Ellison syndrome**, while ileal tumours may cause **carcinoid syndrome** (cutaneous flushing, sweating, bronchospasm, diarrhoea etc. due to released substances including serotonin) especially in the presence of metastatic liver disease (whereby the bioactive products are directly released into the systemic circulation without the 'first-pass effect') or with a large enough tumour burden. The clinical course of NET is quite variable; even low grade NET can metastasize. Most important **prognostic factor** is **location** (midgut most aggressive and often multiple > hindgut/foregut).
- **Gross:** Intramural or submucosal masses that create small polypoid yellow-tan lesions. Often firm (due to desmoplastic reaction) → can cause kinking and small bowel obstruction
- **Histology:** Islands, trabeculae, strands, glands or sheets of uniform cells with round to oval nucleus, 'salt and pepper' chromatin and scant pink cytoplasm. Positive with immunohistochemical stains for neuroendocrine granule markers e.g. Synaptophysin and Chromogranin A

Gastrointestinal stromal tumour (GIST)

- Most common mesenchymal tumour of the abdomen arising from interstitial cells of Cajal of the muscularis propria; more than 50% occur in the stomach
- **Pathogenesis:** ~75-80% have **oncogenic gain-of-function mutations in the tyrosine kinase receptor (TKR) KIT**, while ~8% have **activating mutations in a closely related TKR, platelet-derived growth factor receptor α (PDGFRA)**. KIT and PDGFRA gene mutations are **mutually exclusive** since they act within the same signal transduction pathway to promote tumour cell proliferation and survival. Both sporadic and germline mutations result in constitutively active KIT or PDGFRA TKR. Mutation of KIT or PDGFRA is an early event in sporadic GISTs and alone are insufficient for tumorigenesis. GISTs without KIT or PDGFRA mutations have mutations in other genes that function in these pathways (NF1, BRAF, HRAS, NRAS). Patients may also have germline loss of function mutations in genes encoding components of the mitochondrial succinate dehydrogenase complex (SDHA/B/C/D), which confer an increased risk for GIST and paraganglioma (Carney-Stratakis syndrome)
- **Clinical features:** Usually in adults ~60 yo, uncommonly in children (some of which are related to **Carney triad**, a nonhereditary syndrome seen primarily in young females that includes gastric GIST, paraganglioma and pulmonary chondroma, or **Neurofibromatosis (NF) type 1**). Patients can be asymptomatic or symptomatic related to mass effect or mucosal ulceration causing blood loss/anemia. **Treatment:** if resectable \rightarrow complete surgical resection. If not resectable, those with KIT or PDGFRA mutations often respond to tyrosine kinase inhibitor imatinib. Development of imatinib-resistance can occur due to secondary KIT or PDGFRA mutations. **Prognosis:** correlates with tumour size, mitotic index and location. Metastasis usually to liver or as multiple peritoneal nodules
- **Gross:** usually solitary, well-circumscribed fleshy mass covered by ulcerated or intact mucosa; may also bulge out towards serosa. Cut surface has a whorled appearance
- **Histology:** Spindle cell or epithelioid type or mixed. Immunohistochemical expression of KIT/CD117 (detectable even for those without the mutation) or DOG1

IV. SMALL INTESTINE AND COLON

- Main functions: Nutrient and water transport \rightarrow dysfunction causes malabsorption and diarrhoea
- Immune system interfaces with a diverse array of antigens present in food and gut microbes \rightarrow infectious and inflammatory disorders
- Colon is also a frequent site of gastrointestinal tumours

Intestinal obstruction

- Can occur at any level, but frequently small intestine because of its relatively narrow lumen
- **Causes:** Hernias (most frequent cause worldwide), intestinal adhesions, intussusception, volvulus, and more rarely, tumours, infarction and other causes of strictures e.g. Crohn disease
- **Clinical presentation:** abdominal pain and distension, vomiting and constipation. May be complicated by bowel perforation \rightarrow surgical emergency

Hernia sac: protrusion of a serosa-lined pouch of peritoneum through any weakness or defect in the abdominal wall e.g. inguinal/femoral canal, umbilicus or surgical scar site ('**external** herniation'). The pouch may contain viscera that may become **entrapped**, causing **obstruction**. Pressure at neck of the pouch may further impair venous drainage of the entrapped viscus, resulting in stasis and oedema, increasing the bulk of the herniated loop, leading to permanent entrapment (**incarceration**), arterial and venous compromise (**strangulation**) and **infarction**

Adhesions: fibrous bridges that can develop between bowel segments, abdominal wall or other sites. Usually acquired (e.g. due to previous surgery, infection or other causes of peritoneal inflammation e.g. endometriosis) but can rarely be congenital. Adhesions can cause bowel kinking or form closed loops through which other viscera may slide and become entrapped ('**internal** herniation')

Volvulus: twisting of a loop of bowel about its mesenteric point of attachment, resulting in both luminal and vascular compromise (i.e. obstruction and infarction). Most often occurs in large redundant loops of the sigmoid colon, followed by caecum, small bowel, stomach or transverse colon

Intussusception: when a segment of intestine, constricted by a wave of peristalsis, telescopes into the immediately distal segment. Once trapped, the invaginated segment is further propelled by peristalsis and pulls the mesentery along. May progress to intestinal obstruction as well as compression of mesenteric vessels (infarction). **Most common cause of IO in children <2yo**, where it is usually idiopathic with no underlying anatomical cause and can be resolved by enemas. In older children and adults, it may be due to reactive hyperplasia of Peyer's patches which acts as the leading edge of the intussusception, or an intraluminal mass or tumour requiring surgery

Ischaemic bowel disease

- Majority of GI tract supplied by celiac, superior mesenteric and inferior mesenteric arteries (SMA and IMA), with collateral supplies from the proximal celiac and distal pudendal and iliac circulations. Disease extent depends on (1) severity of vascular compromise, (2) the time frame during which it develops (acute compromise vs chronic progressive hypoperfusion) and (3) vessels affected
- Particularly vulnerable regions of the GIT:
 - Intestinal segments at the end of their respective arterial supplies ('**watershed zones**') i.e. **splenic flexure** (where the SMA and IMA circulations terminate), and **rectosigmoid colon** (where the IMA, pudendal and iliac arterial circulations end). Even generalized hypotension / hypoxemia can cause localized injury at these areas ('focal colitis')
 - **Surface epithelium** (relative to the crypts) as intestinal capillaries run alongside the glands from crypt to surface before making a hairpin turn to empty into the post-capillary venules. This vascular supply protects the epithelial stem cells located within the crypts
- **Risk factors:** (*systemic*) coexisting cardiac or vascular disease, therapeutic vasoconstrictors, some illicit drugs e.g. cocaine, (*localized*) CMV infection causing endothelial damage and small vessel occlusion, strangulated hernia. Specific causes include:
 - *Acute arterial obstruction:* severe atherosclerosis, aortic aneurysm, hypercoagulable states, oral contraceptive use, embolization of cardiac vegetations or aortic atheromas

- *Intestinal hypoperfusion*: cardiac failure, shock, dehydration, vasoconstrictive drugs, systemic vasculitides e.g. polyarteritis nodosa
- *Mesenteric venous thrombosis*: inherited or acquired hypercoagulable states, invasive neoplasms, cirrhosis, trauma or abdominal masses that compress the portal drainage
- **Pathogenesis**: 2 phases - (1) **initial hypoxic injury at the onset** of vascular compromise (2) **reperfusion injury**, initiated by restoration of the blood supply. Greatest damage occurs during reperfusion, and if severe may even trigger multiorgan failure. Underlying mechanisms of reperfusion injury may include leakage of gut lumen bacterial products e.g. lipopolysaccharide into the systemic circulation, free radical production, neutrophil infiltration and release of additional inflammatory mediators
- **Clinical features**: Elderly patients, slightly more women. *Acute ischaemia* typically presents with sudden onset of cramping, left lower abdominal pain, a desire to defecate, and bloody diarrhoea. Surgical emergency if there is paralytic ileus or other features of infarction e.g. guarding and rebound tenderness → can be complicated by gram-negative bacteraemia (endotoxic shock) or perforation. *Chronic ischaemia* may mimic inflammatory bowel disease, with episodes of bloody diarrhoea interspersed with periods of healing
- **Gross**: lesions are most often segmental and patchy. Major vessel occlusions tends to cause transmural infarction, while hypoperfusion / partial occlusion cause mucosal / mural infarction only. Mucosa haemorrhagic and may be ulcerated, while the bowel wall is thickened by oedema
 - *Acute arterial obstruction*: transmural infarction with **sharp demarcation** between normal and ischaemic bowel, which appears intensely congested, dusky to purple-red initially. Later, blood-tinged mucus or frank blood accumulates in the lumen, and the wall becomes edematous, thickened and rubbery. Within 1-4 days, coagulative necrosis of the muscularis propria occurs and perforation may occur. Also serositis, with fibrinopurulent exudates
 - *Mesenteric venous thrombosis*: **less abrupt transition** from affected to normal bowel as arterial blood continues to flow for a time. However, impaired venous drainage eventually prevents oxygenated arterial blood from entering the capillaries, resulting in arterial compromise and similar appearance
- **Histology**: atrophy or sloughing of surface epithelium, with normal or hyperproliferative crypts. Bacterial superinfection and enterotoxin release may also induce pseudomembrane formation (resembling *Clostridium difficile*-associated pseudomembranous colitis).
Acute ischaemia: Inflammation initially absent, but neutrophils are recruited within hours of reperfusion. *Chronic ischaemia*: Accompanied by fibrous scarring / hyalinization of the lamina propria, and (rarely) stricture formation

Radiation enterocolitis: radiation-induced vascular injury may produce changes that are similar to ischaemic disease, although it usually also causes epithelial damage

Necrotizing enterocolitis (NEC): acute disorder of small and large intestines that can result in transmural necrosis, possibly partly due to ischaemic injury. Most common acquired GI emergency of neonates

Angiodysplasia

- Lesion characterized by malformed submucosal and mucosal blood vessels, most often in the caecum or right colon, and usually presents after 50yo. Low incidence but **accounts for 20% of major episodes of lower intestinal bleeding**; may be chronic and intermittent or acute and massive
- **Pathogenesis**: attributed to mechanical and congenital factors. Normal distension and contraction may intermittently occlude the submucosal veins that penetrate through the muscularis propria and lead to focal dilatation and tortuosity of overlying submucosal and mucosal vessels.
- **Histology**: ectatic nests of tortuous veins, venules and capillaries, which may be separated from the intestinal lumen by only the vascular wall and a layer of attenuated epithelial cells → can be easily traumatized resulting in significant bleeding

Malabsorption and diarrhoea

Malabsorption: defective absorption of fat, fat- and water-soluble vitamins, proteins, carbohydrates, electrolytes, minerals, and water, presenting most commonly as chronic diarrhoea

- **Causes**: pancreatic insufficiency, celiac disease, Crohn disease, intestinal graft-vs-host disease
- **Pathogenesis**: malabsorption results from disturbance in at least one of the 4 phases of nutrient absorption: (1) *intraluminal digestion*: proteins, carbohydrates and fats are broken down into forms suitable for absorption (2) *terminal digestion*: hydrolysis of carbohydrates and peptides by disaccharidases and peptidases in the brush border of the small intestinal mucosa (3) *transepithelial transport*: nutrients, fluid and electrolytes are transported across and processed within the small intestinal epithelium (4) *lymphatic transport* of absorbed lipids. A defect in more than 1 process usually contributes although one process may predominate.
- **Clinical symptoms**: Steatorrhoea (hallmark - excessive fecal fat and bulky frothy greasy yellow or clay-coloured stools), weight loss, flatus, anorexia, abdominal distension/pain, muscle wasting, symptoms of vitamin deficiency e.g. anaemia (B12 deficiency), bleeding (vitamin K deficiency) etc.

Diarrhoea: increase in stool mass, frequency or fluidity, typically greater than 200g per day. **Dysentery**: painful, bloody, small-volume diarrhoea

- **Secretory**: isotonic stool; persists during fasting
- **Osmotic**: due to excessive osmotic forces exerted by unabsorbed luminal solutes e.g. with lactase deficiency. Diarrhoea fluid is more concentrated than plasma (hypertonic); abates with fasting
- **Malabsorptive**: generalized failure of nutrient absorption, a/w steatorrhoea; relieved by fasting
- **Exudative**: due to inflammatory disease, characterized by purulent bloody stools; continues during fasting

Cystic fibrosis

- Defect in chloride (+/- bicarbonate ion) secretion due to the absence of the epithelial cystic fibrosis transmembrane conductance regulator (**CFTR**), resulting in defective luminal hydration and thickened secretions. Pancreatic intraductal concretions can form, causing duct obstruction, low

grade chronic autodigestion of the pancreas and eventual **exocrine pancreatic insufficiency** → **malabsorptive diarrhoea**. **Treatment** = oral enzyme supplementation

Celiac disease (aka celiac sprue, gluten-sensitive enteropathy)

- Immune-mediated enteropathy triggered by ingestion of gluten-containing foods e.g. wheat, rye, barley, in genetically predisposed individuals
- **Pathogenesis:** triggered by ingestion of **gluten** (the major storage protein of wheat etc.), of which the alcohol-soluble fraction **gliadin** contains most of the disease-producing components. Some gliadin peptides may induce intestinal epithelial cells to express **IL-15**, triggering activation and proliferation of **CD8+ intraepithelial lymphocytes** which damage the epithelial cells. This may enhance passage of other gliadin peptides into the lamina propria, interact with HLA-DQ2 or HLA-DQ8 on antigen-presenting cells and stimulate CD4+ T cells to produce cytokines that contribute to tissue damage. Malabsorption probably results from this loss of mucosal and brush-border surface area. Increased rates of epithelial turnover, reflected in increased crypt mitotic activity, may also limit the ability of absorptive enterocytes to fully differentiate and express proteins necessary for terminal digestion and transepithelial transport. **Host factors determines whether disease develops**, in particular the **HLA locus** (almost all patients carry the class II HLA-DQ2 or HLA-DQ8 allele). Other genetic factors may include polymorphisms of genes involved in immune regulation and epithelial function, which may also contribute to associations between celiac disease and other immune diseases e.g. T1DM, thyroiditis, Sjogrens syndrome
- **Clinical features:** Bimodal distribution
 - *Adults (30-60 yo), F>M:* present with chronic diarrhoea, bloating, chronic fatigue, anaemia (due to iron and vitamin malabsorption). May have atypical or asymptomatic presentation ('silent' celiac disease = positive serology and villous atrophy without symptoms, or 'latent' celiac disease = positive serology without villous atrophy)
 - *Children, M=F:* classically symptoms occur after introduction of gluten to diet between 6-24 months of age, manifesting as irritability, abdominal distension, anorexia, chronic diarrhoea, failure to thrive, weight loss or muscle wasting. Extraintestinal complaints include arthritis or joint pain, aphthous stomatitis, iron deficiency anemia, delayed puberty and short stature. 10% of patients may have dermatitis herpetiformis, an itchy blistering skin lesion

Diagnostic noninvasive serologic tests (generally performed prior to biopsy): IgA antibodies against tissue transglutaminase (most sensitive), anti-endomysial antibodies. Presence of HLA-DQ2 and DQ8 does not confirm diagnosis, but useful if absent for its negative predictive value

Diagnostic biopsies: usually taken from the 2nd duodenal segment or proximal jejunum, which are exposed to the highest concentrations of dietary gluten

Complications: Risk of malignancy - enteropathy-associated T cell lymphoma (an aggressive lymphoma of intraepithelial T cells), small intestinal adenocarcinoma. Thus, when symptoms of abdominal pain, diarrhoea and weight loss develop despite a strict gluten-free diet, cancer or refractory sprue (in which response to a gluten-free diet is lost) must be considered.

Treatment: gluten-free diet → resolution of symptoms, decreasing titers of anti-tissue transglutaminase antibodies and restoration of mucosal histology within 6-24 months. May also reduce the risk of long-term complications e.g. anaemia and cancer

- **Histology:** Intraepithelial lymphocytosis, crypt hyperplasia and villous atrophy (but not specific: can be seen in other diseases e.g. viral enteritis – correlation with serology is important)

Environmental enteropathy (aka tropical enteropathy / tropical sprue): disorder prevalent in areas and populations with poor sanitation and hygiene, and may contribute to a large number of childhood deaths. Presently no accepted clinical, lab or histopathologic criteria that allows diagnosis. Reported histologic features are more similar to severe celiac disease than infectious enteritis

Autoimmune enteropathy: X-linked disorder characterized by severe persistent diarrhoea and autoimmune disease that occurs most often in young children, caused by FOXP3 gene mutation, resulting in defective function of regulatory T cells

Lactase (disaccharidase) deficiency: Osmotic diarrhoea due to inability to break down or absorb lactase. Can be congenital (rare autosomal recessive disorder caused by mutation in gene encoding lactase) or acquired (common in adults, caused by down-regulation of lactase gene expression, which can develop following enteric viral or bacterial infections and may resolve over time). Defect is biochemical so histology is generally unremarkable

Infectious enterocolitis

Aetiology varies with age, nutrition, and host immune status as well as environmental influences. Paediatric infectious diarrhoea is often caused by enteric viruses, while cholera is common in areas with poor sanitation. Enterocolitis can present with a broad range of symptoms including diarrhoea, abdominal pain, urgency, perianal discomfort, incontinence and dysentery

Bacterial

Cholera: *Vibrio cholerae* (comma-shaped gram-negative bacteria, non-invasive)

- Endemic in India and Bangladesh, with several epidemics in other countries. Primarily water-borne infection (can also be present in food)
- **Cholera toxin** released by the organism causes accumulation of chloride, bicarbonate and sodium within the intestinal lumen, creating an osmotic driving force (**secretory diarrhoea**)
- Most individuals asymptomatic / mild diarrhoea. Severe disease: abrupt onset of watery diarrhoea and vomiting following an incubation period of 1-5 days (voluminous 'rice-water' stools)
- Complications: dehydration, hypotension, shock and death (usually within first 24 hours). Treatment: timely fluid replacement (oral rehydration often sufficient)

Campylobacter enterocolitis: *Campylobacter jejuni* (comma-shaped flagellated gram negative)

- Most common bacterial enteric pathogen in developed countries, cause of **traveler's diarrhoea**. Usually a/w contaminated chicken, also unpasteurized milk or contaminated water
- Bacteria produces toxin and a minority also invade (latter associated with dysentery)
- Most patients have watery diarrhoea, either acute or following an influenza-like prodrome after an incubation period of up to 8 days. Dysentery in 15% of adults and more than 50% in children
- Complications: Reactive arthritis (primarily in patients with HLA-B27), erythema nodosum, Guillain-Barre syndrome. Treatment: Supportive (antibiotics generally not required)

<p>Shigellosis: <i>Shigella sp.</i> (gram negative facultative anaerobe, belongs to <i>Enterobacteriaceae</i> family)</p> <ul style="list-style-type: none"> • One of the most common causes of bloody diarrhoea. Extremely low infective dose → highly transmissible via fecal-oral route (contaminated water/ food). Usually in children <5 yo. • Self-limited disease ~1 week of diarrhoea, fever and abdominal pain. Minority have subacute presentation (several weeks of waxing and waning diarrhoea); mimics new-onset ulcerative colitis
<p>Typhoid fever: <i>Salmonella typhi/paratyphi</i> and Salmonellosis: <i>Salmonella enteritidis</i> etc. (gram negative bacilli of <i>Enterobacteriaceae</i> family)</p> <ul style="list-style-type: none"> • Typhoid fever: person-person transmission or via contaminated food/water. Febrile phase with bacteraemia. Antibiotics can prevent disease progression. • Salmonellosis: Ingestion of contaminated food esp. raw/undercooked meat, poultry, eggs and milk. Vaccines available for both humans and farm animals. Most infections are self-limited.
<p>Escherichia coli: gram-negative bacilli, mostly nonpathogenic but a subset cause human disease</p> <ul style="list-style-type: none"> • Enterotoxigenic E.coli (ETEC): major cause of traveler's diarrhoea; via contaminated food or water • Enteropathogenic E.coli (EPEC): endemic diarrhoea and diarrhoea outbreaks in children <2yo • Enterohaemorrhagic E.coli (EHEC): O157:H7 and non-O157-H7 serotypes; produce Shiga-like toxin • Enteroinvasive E.coli (EIEC): similar to <i>Shigella</i>; invades epithelial cells but do not produce toxin • Enteraggregative E.coli (EAEC): may cause traveler's diarrhoea
<p>Yersinia: <i>Yersinia enterocolitica</i>>> <i>Yersinia pseudotuberculosis</i></p> <ul style="list-style-type: none"> • Ingestion of pork, raw milk and contaminated water. Preferentially involves ileum, appendix and right colon with Peyer patchy and regional lymph node hyperplasia, mimicking acute appendicitis.
<p>Pseudomembranous colitis: morphologic diagnosis (can also be seen in ischaemia or necrotizing infections) but usually caused by <i>Clostridium difficile</i> (anaerobe)</p> <ul style="list-style-type: none"> • Risk factors are advanced age, hospitalization and antibiotic treatment (almost any antibiotic may be responsible). Antibiotics disrupt normal colonic microbiota, allowing <i>C.difficile</i> overgrowth, which releases toxins that lead to epithelial damage. Diagnosis of <i>C.difficile</i>-associated colitis is via detection of the toxin rather than culture. Treatment: Metronidazole or vancomycin. • Pseudomembranes are an adherent layer of inflammatory cells and debris at sites of colonic mucosal injury, that are seen endoscopically as a tan-grey-white coating. Histologically, there is surface epithelial denudation of the colonic mucosa with distension of the superficial portions of the crypts by a mucopurulent exudate ('volcanic eruption') that coalesce to form pseudomembranes
<p>Mycobacterial: <i>Mycobacterium tuberculosis</i>, <i>Mycobacterium bovis</i></p> <ul style="list-style-type: none"> • Intestinal tuberculosis: (primary involvement) drinking of contaminated milk in countries where bovine tuberculosis is present and milk is not pasteurized; or (secondary involvement) caused by swallowing of coughed-up infective material in patients with advanced pulmonary disease • Organisms are seeded to mucosal lymphoid aggregates of small and large bowel, which undergo granulomatous inflammation that can lead to ulceration of the overlying mucosa, esp. ileocaecal region. Healing can cause strictures. Mimics Crohn's disease
<p>Viral</p>
<p>Norovirus: ~50% of all gastroenteritis outbreaks worldwide, usually related to contaminated food or water. Sporadic cases usually due to person-person transmission. Self-limiting disease</p>
<p>Rotavirus: common cause of severe childhood diarrhoea and diarrhoeal mortality (esp. 6-24 mths age)</p>
<p>Adenovirus: common cause of paediatric diarrhoea and in immunocompromised patients</p>
<p>HSV, CMV: systemic infections that can also infect the GIT</p>
<p>Parasitic</p>
<p>Nematodes (roundworms Ascaris and Strongyloides, hookworms and pinworms), cestodes (flatworms and tapeworms), trematodes (flukes)</p>
<p>Protozoa: Entamoeba histolytica (amebiasis)</p>

- Fecal-oral transmission. Mostly affects the caecum and ascending colon. Causes dysentery
- Amoeba attach to the colonic epithelium, induce apoptosis, invade crypts and burrow laterally creating a 'flask-shaped' ulcer. Parasites can also penetrate splanchnic vessels and embolize to the liver to produce abscesses in ~40% of patients

Protozoa: Giardia lamblia (giardiasis)

- Most common parasitic pathogen in humans; spread by fecally contaminated water or food. Presentation can be subclinical or acute/chronic diarrhoea, malabsorption and weight loss
- Identified in duodenal biopsies as pear-shaped organisms tightly bound to the brush border of villous enterocytes. No invasion.

Protozoa: Cryptosporidium parvum (cryptosporidiosis)

- First discovered as a cause of chronic diarrhoea in AIDS patients; also a cause of acute self-limited diarrhoea or persistent diarrhoea in immunocompetent hosts. Usu. via contaminated drinking water
- Usually identified in terminal ileum and proximal colon. Intracellular, epithelial apical membrane

Fungal

Candida, Aspergillus, Mucormycosis, Histoplasma: systemic infections that can affect the GIT

Irritable bowel syndrome (IBS)

Chronic relapsing abdominal pain, bloating and changes in bowel habits, but normal gross and microscopic evaluation – diagnosis depends on clinical symptoms and functional testing. Pathogenesis is poorly defined, with interplay between psychological stressors, diet, perturbation of the gut microbiome, increased enteric sensory responses to gastrointestinal stimuli and abnormal GI motility. Not associated with serious long-term sequelae; prognosis is most closely related to symptom duration, with longer duration correlating with reduced likelihood of improvement

Inflammatory bowel disease (IBD)

- Chronic inflammation of the GI tract resulting from inappropriate mucosal immune activation, usually referring to either **Ulcerative Colitis (UC)** or **Crohn Disease (CD)**
- **Pathogenesis:** Likely due to combined effects of alterations in host interactions with intestinal microbiota, intestinal epithelial dysfunction, aberrant mucosal immune responses and altered composition of the gut microbiome
 - **Genetics:** risk of disease is increased when there is an affected family member. Over 160 IBD-associated genes have been identified, with each gene conferring only a small increase in risk e.g. *NOD2* (for CD) which is involved in recognition and response to intracellular pathogens (supporting the hypothesis that inappropriate immune reactions to luminal bacteria are an important component of IBD pathogenesis)
 - **Mucosal immune responses:** T helper cells are activated in Crohn disease (response polarized to the TH1 type; TH17 cells most likely contribute to disease pathogenesis). Many other pro-inflammatory cytokines including TNF and immunoregulatory molecules e.g. IL-10 also appear to play a role. Immunosuppressive agents remain the mainstay of treatment

- **Epithelial defects:** defects in intestinal epithelial tight junction barrier function in CD (a/w specific disease-associated *NOD2* polymorphisms); inhibition of matrix metalloproteinase 9 in UC (a/w polymorphisms involving *ECM1*)
- **Microbiota:** as mentioned earlier, linkage to *NOD2* points to the involvement of microbes in the causation of CD. The presence of antibodies against bacterial proetin flagellin are also seen in CD. Clinical trials suggest that probiotic bacteria or even fecal microbial transplants from healthy individuals may benefit IBD patients

It has been theorized that IBD is a result of a **self-amplifying cycle** that gives rise to maladaptive and injurious immune responses, by which transepithelial flux of luminal bacterial components activates innate and adaptive immune responses. In a genetically susceptible host, the subsequent release of TNF and other immune-mediated signals direct the epithelium to increase tight junction permeability, causing further increase in the influx of luminal material, resulting in a vicious cycle. The **hygiene hypothesis** suggests improved food storage conditions, decreased food contamination and changes in gut microbiome composition results in inadequate development of regulatory processes that limit mucosal immune responses. This in turn allows some mucosa-associated microbial organisms to trigger persistent and chronic inflammation in susceptible hosts

- **Clinical features:** Teens and young adults. Caucasians but increasing incidence in other regions e.g. Africa, South America and Asia. Distinction between CD and UC is based largely on the **distribution of affected sites** and **morphologic expression of disease** at these sites. **Extraintestinal manifestations** may also be present.

Crohn disease	Ulcerative colitis
Recurrent granulomatous, fibrosing inflammatory disorder affecting terminal ileum (or colon) +/- other systemic manifestations	Recurrent acute-on-chronic ulcero-inflammatory disease affecting mainly rectum and distal colon
Clinical features	
Relapsing disorder: intermittent attacks of (bloody) diarrhoea with stringy mucoid material, lower abdominal pain, cramps that are temporarily relieved by defecation +/- fever; can also present acutely. Asymptomatic periods may last for weeks to months	
Disease re-activation by triggers include physical or emotional stress, specific dietary items and cigarette smoking (a strong exogenous risk factor for development of Crohn disease; initiation of smoking may be associated with disease onset but smoking cessation does not result in disease remission)	Triggers may include episode of infectious enteritis, psychological stress, after smoking cessation
Extraintestinal manifestations: uveitis, ankylosing spondylitis, migratory polyarthritis	Similar; also primary sclerosing cholangitis (PSC)
Saccharomyces cerevisiae antibodies positive	pANCA+ (75%)
Complications	
Fistulae between bowel loops and with other organs e.g. bladder, vagina, skin (esp. perianal); perforations and peritoneal abscesses	Nil
Fibrosing strictures (particularly of the terminal ileum; require surgical resection)	Nil

Common recurrence after surgery	No. Colectomy cures intestinal disease (although extraintestinal manifestations may persist)
Fat/vitamin malabsorption, iron deficiency and hypoalbuminaemia (in extensive small bowel disease)	Nil
Increased malignancy risk (in colonic disease)	Yes
No toxic megacolon	Toxic megacolon occurs due to damage of the muscularis propria by inflammatory mediators, and disturbance of neuromuscular function. Significant risk of perforation
Gross and microscopy	
Skip lesions (i.e. separate sharply delineated areas of disease)	Diffuse continuous involvement. Rarely 'caecal patch' in L-sided UC
Frequently ileum ; any other area of the GI tract	Disease limited to Rectum +/- part or all of colon . Small intestine normal apart from mild mucosal inflammation of the distal ileum ('backwash ileitis') in severe pancolitis
Transmural inflammation and oedema – thickened wall with marked fibrosis +/- strictures . In extensive transmural disease, serositis and mesenteric fat extending around the serosal surface ('creeping fat')	Mucosa +/- submucosa – usually thin wall, mild or no fibrosis / serositis; strictures are rare
' Cobblestone ' appearance of mucosa (due to patchy sparing of mucosa interspersed with deep ulcers)	Slightly red granular friable mucosa; Frequent mucosal pseudopolyps (isolated islands of regenerating mucosa that bulge into lumen amongst broad-based ulcers). Mucosal atrophy in chronic disease with a flat and smooth mucosal surface that lacks normal folds
Aphthous ulcer (earliest lesion) → coalesce into elongated serpentine ulcers oriented along the axis of the bowel. Deep fissuring ulcers between mucosal folds, with fistulae/sinuses/perforation	Superficial broad-based ulcers along the long axis of the colon; no fistula/sinuses
Microscopy: Active chronic colitis	
Activity: cryptitis, crypt abscesses (clusters of neutrophils within crypts), erosions, ulceration Chronicity: distortion of mucosal architecture due to repeated cycles of crypt destruction and regeneration, epithelial metaplasia (pseudopyloric metaplasia and (in the left colon) Paneth cell metaplasia), crypt atrophy/shortening	
Non-caseating granulomas (~35% of cases) is the hallmark – may occur in areas of active disease, or uninvolved regions in any layer of the intestinal wall or mesenteric lymph nodes	Nil

Indeterminate colitis: ~10% of IBD patients without definitive features of either UC or CD. Serologic studies for p-ANCA (UC) and antibodies to *Saccharomyces cerevisiae* (CD) may help differentiate, but despite diagnostic uncertainty, patients with indeterminate colitis often still can be treated effectively due to extensive overlap in medical management of UC and CD

Colitis-associated neoplasia

- One of the most feared long-term complications of UC and colonic CD
- Risk of dysplasia is related to: (i) duration of disease (risk increases sharply 8-10 years after disease onset); (ii) extent of disease (patients with pancolitis are at greater risk than those with only L-sided disease); (iii) nature of the inflammatory response (greater frequency and severity of active inflammation confers increased risk)
- To facilitate early detection of neoplasia, patients usually undergo frequent endoscopic surveillance approximately 8 years after diagnosis of IBD (earlier for patients with both IBD and PSC who have even greater risk of developing cancer). The goal of surveillance biopsies is to identify dysplastic epithelium, which is a precursor to colitis-associated carcinoma. Dysplasia can occur in flat areas of mucosa that are not grossly recognized as abnormal. Dysplasia can be low grade or high grade, and may be multifocal. Sporadic colonic adenomas can also occur in IBD patients and may be difficult to distinguish from polypoid foci of IBD-associated dysplasia. Treatment depends on the distinction as IBD-associated dysplasia may prompt colectomy due to association with invasive carcinoma while sporadic adenomas can be excised via polypectomy.

Diversion colitis

- Inflammation developing in a segment of colon diverted away from the normal faecal flow e.g. in surgical treatment of intestinal disorders (like UC) which may require creation of a temporary or permanent ostomy and a blind distal segment of colon
- **Pathogenesis:** Not well understood; possibly due to changes in the luminal microbiota and diversion of the fecal stream that provides nutrients to colonic epithelial cells. **Treatment:** enemas containing short-chain fatty acids, a product of bacterial digestion in the colon and an important energy source for colonic epithelial cells, can promote mucosal recovery in some cases. Ultimate cure is re-anastomosis of the diverted segment. **Histology:** Numerous mucosal lymphoid follicles. In severe cases, may mimic IBD (crypt abscesses, mucosal architectural distortion or rarely granulomas)

Microscopic colitis

- Idiopathic disease, presenting with chronic non-bloody watery diarrhoea and with normal radiologic and endoscopic findings. Encompasses 2 entities: **collagenous colitis** and **lymphocytic colitis**
- **Collagenous colitis:** middle-aged and older women; characterized by a dense subepithelial collagen layer +/- increased numbers of intraepithelial lymphocytes
- **Lymphocytic colitis:** strong association with celiac disease and autoimmune disease; increased intraepithelial lymphocytes (>20 T-cells per 100 colonocytes)

Graft vs host disease

- Occurs following haematopoietic stem cell transplantation, usually involving small bowel and colon. Presents as watery diarrhoea but may become bloody in severe cases

- Occurs secondary to donor T cells targeting antigens on the recipient's GI epithelial cells. Histology shows epithelial apoptosis (particularly of the crypt cells) with sparse inflammation in the lamina propria. Rarely, total gland destruction occurs

Diverticular disease

- Acquired pseudodiverticular outpouchings of colonic mucosa and submucosa (unlike true diverticula e.g. Meckel diverticulum, which includes all 3 layers of the colonic wall). Usually multiple (**diverticulosis**)
- **Pathogenesis:** results from the **elevated intraluminal pressure** usually in the sigmoid colon (probably due to exaggerated peristaltic contractions with spasmodic sequestrations of bowel segments, which may be enhanced by diets low in fiber which reduce stool bulk, particularly in the sigmoid colon). This **causes outpouchings in the focal discontinuities in the colonic muscle wall** where nerves, arterial vasa recta and their connective tissue sheaths penetrate the inner circular muscular coat. The external longitudinal layer of the MP is unable to reinforce these gaps as they are gathered into the 3 bands (taenia coli) in the colon
- **Clinical features:** Prevalence increases with age (common in those over 60yo); less common in Japan and developing countries ? dietary differences. R-sided disease more common in Asia but uncommon in Western countries. Most individuals are asymptomatic, but ~20% present with intermittent cramping, continuous lower abdominal discomfort, constipation, distension, sensation of incomplete defecation or occasionally chronic / intermittent per rectal bleeding (with erosion into blood vessels). **Complications:** Obstruction of diverticula leads to inflammation, resulting in **diverticulitis and peri-diverticulitis**, which can lead to perforation, pericolic abscesses, sinus tracts, fistulae and occasionally peritonitis. Diverticulitis may also cause segmental diverticular disease-associated colitis (SCAD), fibrotic thickening in and around the colonic wall or stricture formation. **Treatment:** Increased dietary fiber may help symptoms. Even when diverticulitis occurs, it most often resolves spontaneously; relatively few patients require surgical intervention
- **Gross:** small flask-like outpouchings ~0.5-1 cm in diameter that occur alongside the taenia coli
- **Histology:** thin wall composed of flattened / atrophic mucosa, compressed submucosa and attenuated or totally absent muscularis propria. Hypertrophy of the circular layer of the muscularis propria in the affected bowel segment is common

Polyps

- Gross morphology: sessile (broad-based) vs pedunculated (narrow base +/- stalk)
- Non-neoplastic (inflammatory, hamartomatous or hyperplastic) vs neoplastic (usually adenoma)

Non-neoplastic polyps

- **Hyperplastic:** benign epithelial proliferations, usually in left colon, often multiple. Serrated surface architecture (serrations restricted to upper third of the crypt)
- **Inflammatory:** can form as part of the solitary rectal ulcer syndrome due to impaired relaxation of the anorectal sphincter, leading to recurrent abrasion and ulceration of the overlying rectal mucosa; an inflammatory polyp develops as a result of the chronic cycles of injury and healing. Entrapment of

the polyp in the fecal stream subsequently leads to mucosal prolapse. Histology = mixed inflammatory infiltrates, surface erosion, and epithelial hyperplasia +/- lamina propria fibromuscular hyperplasia (in mucosal prolapse)

- **Hamartomatous:** occur sporadically or as part of various genetically determined or acquired syndromes (some of which are associated with increased cancer risk either within the polyps or at other intestinal or extra-intestinal sites)
 - **Juvenile polyps:** morphology of sporadic vs syndromic forms are indistinguishable. Usually in children <5 yo, in the rectum and typically present with PR bleeding. Sporadic juvenile polyps are usually solitary (aka 'retention polyps') and rarely associated with dysplasia, while individuals with the AD syndrome of juvenile polyposis have multiple in the colon, may have dysplasia both within the juvenile polyp and in separate adenomas, and may also have polyps in the stomach and small bowel that can undergo malignant transformation. **Histology:** dilated cystic glands filled with mucin and inflammatory debris within an inflamed oedematous lamina propria. Most common mutation is *SMAD4* and *BMPRI1A* in the TGF- β signaling pathway.
 - **Peutz-Jeghers syndrome:** AD syndrome due to germline loss-of-function mutations in the tumour suppressor gene *STK11*, presents at a median age of 10-15 yo with multiple GI hamartomatous polyps and mucocutaneous hyperpigmentation (including buccal mucosa). PJ polyps can be complicated by intussusception. PJS is associated with a markedly increased risk of several malignancies e.g. colon (can develop at sites without PJ polyps), breast, lung, pancreas and thyroid – regular surveillance is thus recommended. Most PJ polyps are in the small intestine, large and pedunculated. **Histology:** characteristic arborizing network of connective tissue, smooth muscle, lamina propria and glands lined by normal-appearing intestinal epithelium

Neoplastic: any neoplastic mass lesion in the GI tract may produce a mucosal protrusion or polyp, including adenocarcinoma, neuroendocrine tumours, stromal tumours, lymphomas and even metastatic cancers from distant sites. Most common neoplastic polyps are **colonic adenomas**, which are precursors to the majority of colorectal adenocarcinomas

- Adenomas are intraepithelial neoplasms, ranging from small often pedunculated polyps to large sessile lesions, characterized by the presence of **epithelial dysplasia**. Dysplasia is characterized by cytologic and architectural atypia, and can be low grade or high grade
- Although they are precursor lesions, the majority of adenomas do not progress to become adenocarcinomas, and it may be that transformation is stochastic, being dependent on acquisition of oncogenic mutations merely by chance. A small proportion of adenomas may harbour invasive cancer at the time of detection; risk of malignancy is greater with **size, presence of high grade dysplasia, higher proportion of villous architecture and increased numbers of adenomas**. Most adenomas are clinically silent, with the exception of large polyps that produce occult bleeding and anaemia and rare villous adenomas that cause hypoproteinemic hypokalemia by secreting large amounts of protein and potassium. Therefore, regular surveillance colonoscopy and polyp removal is needed to reduce the incidence of colorectal adenocarcinoma

- **Histology:** Conventional adenomas are classified as tubular, tubulovillous or villous based on their architecture. Other forms include serrated adenomas e.g. traditional serrated adenomas, sessile serrated lesion/polyp

Colorectal cancer syndromes

Adenomatous polyposis syndromes like FAP and non-polyposis syndromes like HNPCC typify distinct pathways of neoplastic transformation and progression that also contribute to the majority of sporadic colon cancers

Adenomatous polyposis

- **Familial adenomatous polyposis (FAP):** AD disorder in which patients develop numerous colorectal adenomas as teenagers, caused by **mutations of the adenomatous polyposis coli (APC) gene in chr5q21**, a key negative regulator of the Wnt signaling pathway. Classic FAP require at least 100 polyps. The polyps are morphologically indistinguishable from sporadic adenomas, although flat or depressed adenomas as well as microscopic adenomas consisting of only 1 or 2 dysplastic crypts are also frequently observed in otherwise normal-appearing mucosa. Colorectal adenocarcinoma develops in 100% of untreated FAP patients, often below age 30 and nearly always by age 50. Prophylactic colectomy is thus the standard treatment for individuals with APC mutations, although there remains a risk for neoplasia at other sites e.g. stomach and ampulla of Vater. Variants: Gardner syndrome and Turcot syndrome (associated with other extraintestinal manifestations)
- **MYH-associated polyposis:** AR disorder with bi-allelic mutations of the base-excision repair gene *MYH*; colonic phenotype is similar to attenuated FAP, with polyp development at later ages, fewer than 100 adenomas and delayed appearance of colon cancer (usually later than 50yo). Serrated polyps with KRAS mutations are also frequently present

Hereditary non-polyposis colorectal cancer (HNPCC) / Lynch Syndrome (LS)

- Most common syndromic form of colon cancer (2-4% of all colorectal cancers)
- AD; caused by inherited mutations in genes that encode **mismatch repair proteins (MMR)** (responsible for the detection, excision and repair of errors that occur during DNA replication). Defects in mismatch repair lead to the accumulation of mutations at rates up to 1000 times higher than normal, mostly in regions containing short repeating sequences referred as microsatellites (**microsatellite instability**)
- HNPCC refers to the *clinical phenotype* of familial colon cancer; LS refers to individuals with (*genetic germline MMR mutation*). Patients with LS have increased risk of extra-colonic malignancies
- Colon cancers tend to occur at younger ages than sporadic colon cancers, often right sided. Extra-colonic malignancies include endometrium, stomach, ovary, ureters, brain, hepatopancreatobiliary tract, small bowel and skin
- Important to identify these patients because of the implications for genetic counselling, the elevated risk of a second malignancy of the colon or other organs, and differences in prognosis and therapy

Colorectal adenocarcinoma (CRC)

- Nearly all colonic cancers are adenocarcinomas. It is the most common GI tract malignancy and a major cause of morbidity and mortality worldwide (10% of all cancer deaths). In contrast, the small intestine is an uncommon site for benign and malignant tumours despite accounting for 75% of the overall length of the GI tract
- **Risk factors:** Diet – increased risk with **low intake of unabsorbable vegetable fiber and high intake of refined carbohydrates**. It is believed that reduced fiber content leads to decreased stool bulk and altered composition of the intestinal microbiota, which may increase synthesis of potentially toxic oxidation by-products of bacterial metabolism, which would be expected to remain in contact with the colonic mucosa for longer periods of time as a result of reduced stool bulk. **High fat intake** also enhances hepatic synthesis of cholesterol and bile acids, which can be converted into carcinogens by intestinal bacteria. Epidemiologically, the incidence of CRC is highest in North America, is common in Australia, New Zealand, Europe and increasingly Japan with changes in lifestyle and diet.
- **Pharmacologic chemoprevention:** epidemiologic studies suggest that aspirin or other NSAIDS have a protective effect, possibly mediated by inhibition of the enzyme cyclooxygenase-2 (COX-2), which is highly expressed in 90% of colorectal carcinomas and 40-90% of colorectal adenomas. COX2 is necessary for production of prostaglandin E2, which promotes epithelial proliferation, particularly after injury
- **Pathogenesis:** heterogeneous combination of molecular events that includes genetic and epigenetic abnormalities, resulting in the **stepwise accumulation of multiple mutations**. At least 2 genetic pathways:
 - (1) **APC/b-catenin pathway (80% of sporadic colon tumours):** activated in the classic adenoma-carcinoma sequence; chromosomal instability is the hallmark (Vogelstein's hypothesis)
 - Typically includes **APC gene mutation** (chr 5q21) early in the neoplastic process. Both copies of APC must be functionally inactivated, either by mutation or epigenetic events, for adenomas to develop. APC is a key negative regulator of b-catenin, a component of the Wnt signaling pathway. The APC protein normally binds to and promotes degradation of b-catenin. With loss of APC function, b-catenin accumulates and translocates to the nucleus, where it forms a complex with the DNA-binding factor TCF and activates the transcription of genes, including *MYC* and *cyclin D1*, that promote proliferation. Colon cancers without APC mutations harbour b-catenin mutations that allow them to avoid APC-dependent degradation, thereby having the same impact as loss of APC function
 - Additional mutations accumulate, including **activating KRAS mutations** that promote growth and prevent apoptosis (often a late event in carcinoma development), **mutations in other tumour suppressor genes** e.g. *SMAD2* and *SMAD4* (effectors of TGF- β signalling), *TP53* (mutated in 70-80% of colon cancers, probably a late event in carcinoma development). Loss of functions of these genes are often caused by chromosomal deletions, but may also be silenced by methylation of a CpG-rich zone (or CpG island), a 5' region of some genes that frequently includes the promoter and transcriptional start site
 - Expression of **telomerase** also increases as lesions become more advanced

- (2) **Microsatellite instability (MSI) pathway:** associated with defects in DNA mismatch repair and accumulation of mutations in microsatellite repeat regions of the genome (MSI-high tumours)
- Some microsatellite sequences are located in the coding or promoter regions of genes involved in regulation of cell growth e.g. TGFR- β receptor and the pro-apoptotic protein BAX, contributing to uncontrolled cell growth and enhanced survival of tumour cells
 - MSI-H tumours can be identified by **loss of immunohistochemical staining for mismatch repair (MMR) proteins** (MLH1, MSH2, MSH6 and PMS2) or by **molecular genetic analysis of microsatellite sequences**
 - These tumours often have prominent mucinous differentiation and peritumoral lymphocytic infiltrates, and are frequently in the R colon
- (3) A subset of **microsatellite unstable** colon cancers **without** mutations in DNA mismatch repair enzymes demonstrate the **CpG island hypermethylation phenotype (CIMP)**. In these tumours, the MLH1 promoter region is typically hypermethylated, thereby reducing MLH1 expression and repair function. **Activating mutations in the oncogene BRAF** are common in these cancers, while *KRAS* and *TP53* (seen in the chromosomal instability pathway) are not typically mutated
- (4) A small group of colon cancers display **increased CpG island methylation in the absence of microsatellite instability**. Many of these tumours harbour ***KRAS* mutations**, but *TP53* and *BRAF* mutations are uncommon. In contrast, *TP53* mutations are common in colon cancers that do not display a CpG island methylator phenotype
- **Clinical features:** Peaks at 60-70 yo. R-sided colon cancers often present with symptoms of iron-deficiency anaemia (fatigue and weakness) while L-sided colon cancers may produce occult bleeding, changes in bowel habits, cramping and left lower quadrant discomfort. As CRCs may be insidious and undetected for long periods, endoscopic screening and polyp removal (as most carcinomas arise within adenomas) is important for cancer prevention. **Prognostic factors:** depth of tumour invasion, presence of lymph node metastases and systemic metastases (AJCC TNM staging), and poor histologic differentiation. Systemic metastases frequently include liver due to portal drainage of the colon (except for rectum - does not drain via portal circulation), lung and bones. However, regardless of stage, some patients may still do well for years following resection of solitary or oligometastatic tumour foci
 - **Gross:**
 - *Proximal colon:* polypoid exophytic masses; because the caecum and ascending colon are of large caliber, they rarely cause obstruction
 - *Distal colon:* annular lesions that produce 'napkin-ring' constrictions and luminal narrowing, sometimes to the point of obstruction
 - **Histology:** Both right and left-sided colonic adenocarcinomas are similar. Most tumours are composed of irregular glands, typically cribriform architecture (grade of differentiation depends on extent of gland formation), lined by tall columnar cells with dirty necrotic luminal debris. The invasive component elicits a strong desmoplastic response which is responsible for their firm consistency. Some tumours have abundant mucin, and may be composed of signet-ring cells



V. ANAL CANAL

Anal canal is divided into thirds – the upper zone is lined by columnar rectal epithelium, the middle third by transitional epithelium, and the lower third by stratified squamous epithelium

Haemorrhoids

- Thin-walled dilated submucosal vessels (varices) that protrude beneath the anal or rectal mucosa
 - *External haemorrhoids*: inferior haemorrhoidal plexus located below the anorectal line
 - *Internal haemorrhoids*: superior haemorrhoidal plexus within the distal rectum
- Affect about 5% of the general population and develop secondary to persistently elevated venous pressure within the haemorrhoidal plexus. **Risk factors**: straining at defecation because of constipation, venous stasis of pregnancy, portal hypertension (similar pathogenesis to oesophageal varices – variceal dilations of the anal and perianal venous plexues form collaterals that connect the portal and caval venous systems, thereby relieving the venous hypertension). Usually in older patients (except pregnant ladies). **Complications**: In their exposed position, they can be traumatized and can bleed, become inflamed, ulcerated, thrombosed and recanalized. Patients thus often present with **pain and PR bleed** (bright red blood seen on toilet tissue). **Treatment**: sclerotherapy, rubber band ligation, infrared coagulation or surgical excision (haemorrhoidectomy)

Carcinomas of the anal canal

May have typical **glandular** (adenocarcinoma) or **squamous** (squamous cell carcinoma) patterns of differentiation, recapitulating the normal epithelium of the upper or lower thirds of the anal canal, respectively. Pure squamous cell carcinoma of the anal canal is frequently associated with HPV infection, which also causes precursor lesions e.g. condyloma acuminatum. An additional pattern, **basaloid** pattern, is present in tumours populated by immature cells derived from the basal layer of transitional epithelium

VI. VERMIFORM APPENDIX

Normal true diverticulum of the caecum. Prone to acute and chronic inflammation; tumours (adenocarcinoma, neuroendocrine tumours) can also develop here

Acute appendicitis

- Acute inflammation of the appendix; most common in adolescents, young adults (lifetime risk 7%)
- **Pathogenesis**: thought to be initiated by progressive **increases in intraluminal pressure** that compromise venous outflow. In 50-80% of cases, acute appendicitis is associated with overt **luminal obstruction**, usually caused by a small stone-like mass of stool (faecolith) or less commonly, a gallstone, tumour or mass of worms (oxyuriasis vermicularis). Stasis of luminal contents, which favours bacterial proliferation, triggers ischaemia and inflammatory responses, resulting in tissue oedema and neutrophilic infiltration of the wall

- **Clinical features:** periumbilical pain that subsequently localizes to the right iliac fossa (RIF), associated with nausea, fever, vomiting and mildly elevated peripheral white cell count. Classic physical examination finding is the McBurney sign, deep tenderness located 2/3rd of the distance from the umbilicus to the right anterior superior iliac spine (McBurney point). However, classic signs and symptoms may be absent (esp. in the very young and old) e.g. retrocaecal appendix, malrotated colon. **Clinical differential diagnoses** include mesenteric lymphadenitis (often due to unrecognized Yersinia infection or viral enterocolitis), acute salpingitis, ectopic pregnancy, mittelschmerz (pain caused by minor pelvic bleeding at the time of ovulation) and Meckel diverticulitis. **Complications:** perforation and peritonitis, abscesses / phlegmon, pyelophlebitis, portal venous thrombosis, liver abscess and bacteraemia. **Treatment:** Surgery (appendectomy)
 - **Gross:** Congested turgid oedematous appendix with dull granular erythematous serosa +/- serosal fibrinopurulent exudates. Lumen may contain fecolith or purulent material
 - **Histology:** mucosal ulceration, transmural acute inflammation (involving muscularis propria) +/- focal abscesses within the wall (**acute suppurative appendicitis**), subserosal vascular congestion, acute serositis and serosal fibrinopurulent reaction. Further compromise of appendiceal vessels leads to large areas of haemorrhagic ulceration and gangrenous necrosis that extends to the serosa (**acute gangrenous appendicitis**), which can be followed by rupture and suppurative peritonitis

Tumours of the appendix

- Most common tumour is the **well-differentiated neuroendocrine tumour**, usually discovered **incidentally** at the time of surgery or examination of a resected appendix. Usually at the tip of the appendix, with mostly benign behaviour (very infrequent nodal metastasis; distant spread is exceptionally rare)
- **Conventional adenomas or non-mucin-producing adenocarcinomas** can also occur in the appendix and may cause obstruction and enlargement that mimics acute appendicitis
- **Mucocele:** dilated appendix filled with mucin. This may simply represent an obstructed appendix containing inspissated mucin, or be a consequence of a low grade appendiceal mucinous neoplasm (LAMN) or mucinous adenocarcinoma, whereby involvement of the serosa can lead to intraperitoneal seeding and spread (pseudomyxoma peritonei or mistaken for mucinous ovarian tumours – the abdomen fills with tenacious semisolid mucin)

VII. PERITONEAL CAVITY

Houses the abdominal viscera and is lined by a single layer of mesothelial cells; these cover the visceral and parietal surfaces and are supported by a thin layer of connective tissue to form the peritoneum

- **Sterile peritonitis:** Chemical irritation causing inflammation e.g. due to leakage of bile (e.g. from perforation or rupture of the biliary system) or pancreatic enzymes (e.g. in acute haemorrhagic pancreatitis). **Endometriosis** can cause haemorrhage into the peritoneal cavity where it acts as an

irritant. **Foreign material** introduced surgically also induces foreign body-type granulomas and fibrous scarring e.g. talc, sutures. **Ruptured dermoid cysts** release keratins and also induce an intense granulomatous reaction

- **Infection:** Bacterial peritonitis occurs when bacteria (e.g. *E.coli*) from the GI lumen are released into the abdominal cavity, most commonly following perforation/damage to the bowel. Spontaneous bacterial peritonitis occurs without an obvious source of contamination, seen most often in patients with cirrhosis and ascites and less frequently in children with nephrotic syndrome, possible due to gut translocation of bacteria
- **Sclerosing retroperitonitis** (idiopathic retroperitoneal fibrosis): characterized by dense fibrosis that may extend to involve the mesentery. Many cases through to be related to IgG4-related sclerosing disease, an immune-inflammatory disorder that can lead to fibrosis in a wide variety of tissues
- **Tumours:** (*Primary*) **Mesotheliomas** are malignant tumours arising from the peritoneal lining, similar to tumours of the pleura and pericardium. Peritoneal mesotheliomas are almost always associated with significant asbestos exposure. Rarely, primary benign and malignant soft tissue tumours may also develop within the peritoneum and retroperitoneum e.g. desmoplastic small round cell tumour. (*Secondary*) Tumours from other primary sites may involve the peritoneum by direct spread or metastatic seeding, resulting in **peritoneal carcinomatosis**. Mucinous carcinomas particularly of the appendix may cause pseudomyxoma peritonei