Small bowel: anatomy & physiology

**with a touch of clinical application*

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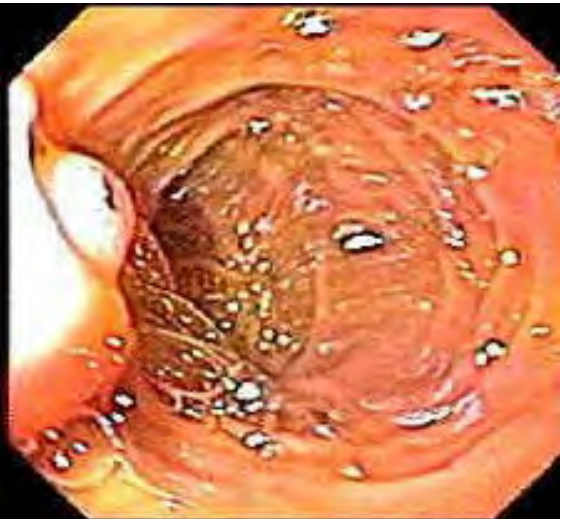
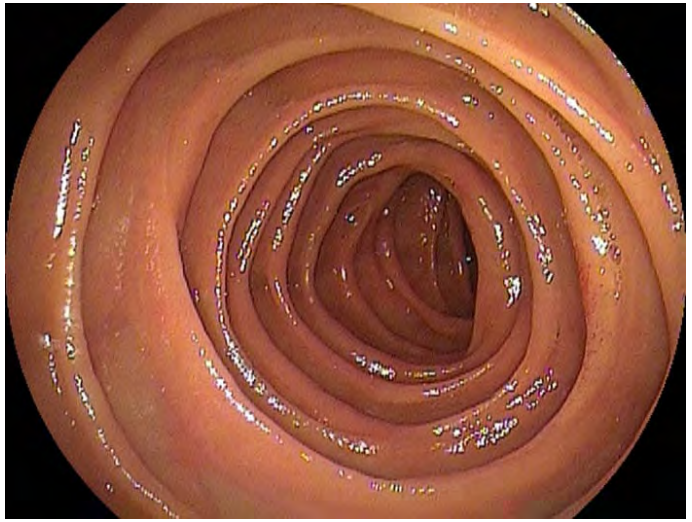
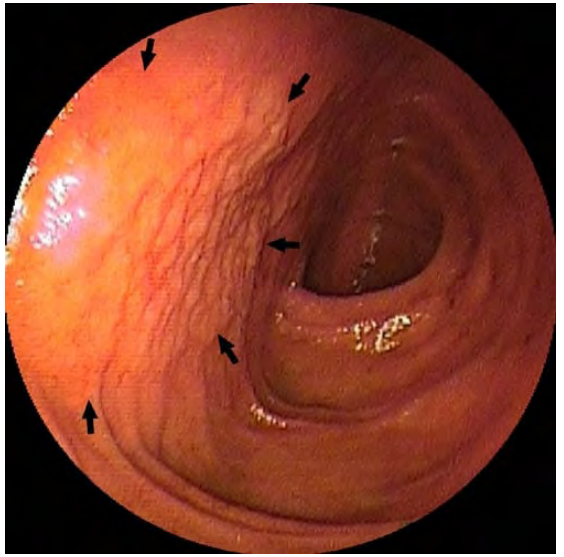
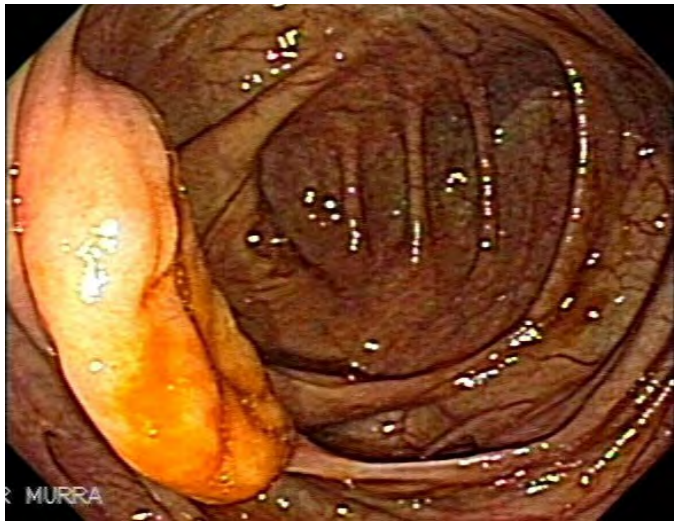
June 2026

Overview

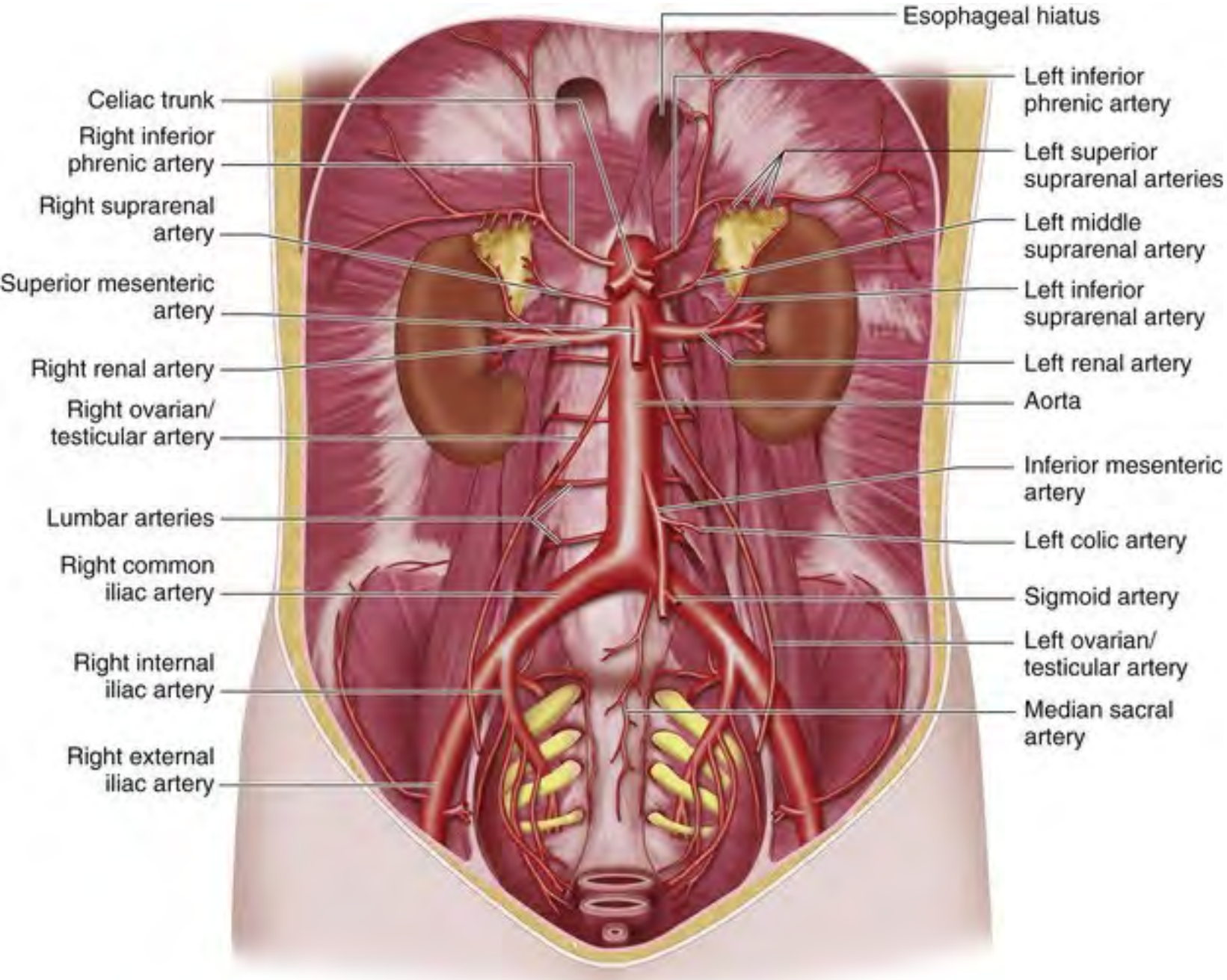
- Macroanatomy
- Vascular supply & drainage
- Lymphatics
- Neural innervation
- Microanatomy
- Function
  - Digestion - electrolytes & fluids - micronutrients
  - Barrier - immune surveillance - gut hormones
- Clinical application

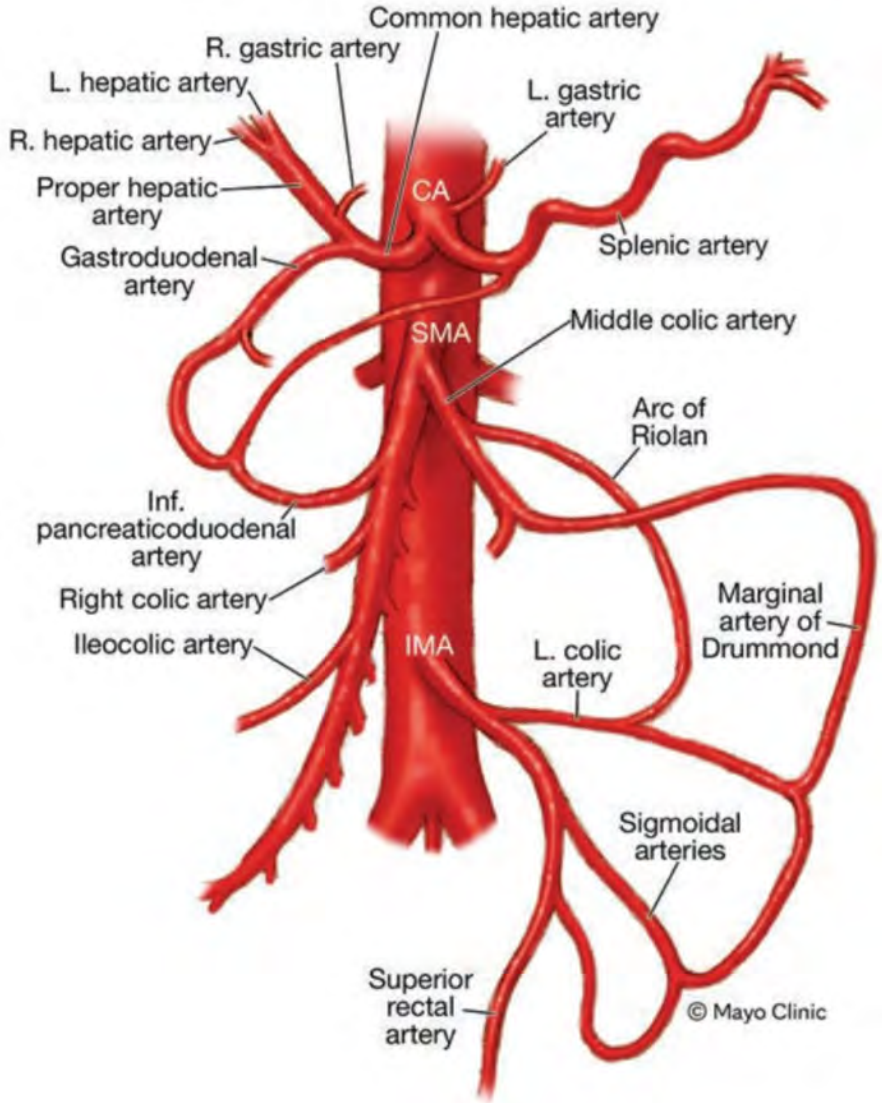
- Stomach-**Duodenum-Jejunum-Ileum**-Colon
  - 3-8.5m long with fx surface area 30-40m^2

Embryology

- Small intestines arises from the midgut along with
  - SMA
  - Proximal colon (up to prox 2/3 of TC)
  - Communicates with omphalomesenteric duct – Meckel's diverticulum
  - Eventually rotates 270' anticlockwise around SMA axis
    - Failure leads to malrotation: volvulus, SMA obstruction
- Caudal foregut prox duodenum (pylorus – major duo papilla)
- Hindgut = Lt colon
- Mid vs hindgut relevant molecular genetics
  - Rt/mid: MSI-high (immunotherapy); CIMP, BRAF, serrated neoplasia, Lynch, poor diff with poorer prognosis with mets
  - Lt/hind: APC, KRAS, TP53, better anti-EGFR response (RAS wild-type)


Esophageal hiatus
Celiac trunk
Right inferior phrenic artery
Right suprarenal artery
Superior mesenteric artery
Right renal artery
Right ovarian/ testicular artery
Lumbar arteries
Right common iliac artery
Right internal iliac artery
Right external iliac artery
Left inferior phrenic artery
Left superior suprarenal arteries
Left middle suprarenal artery
Left inferior suprarenal artery
Left renal artery
Aorta
Inferior mesenteric artery
Left colic artery
Sigmoid artery
Left ovarian/ testicular artery
Median sacral artery

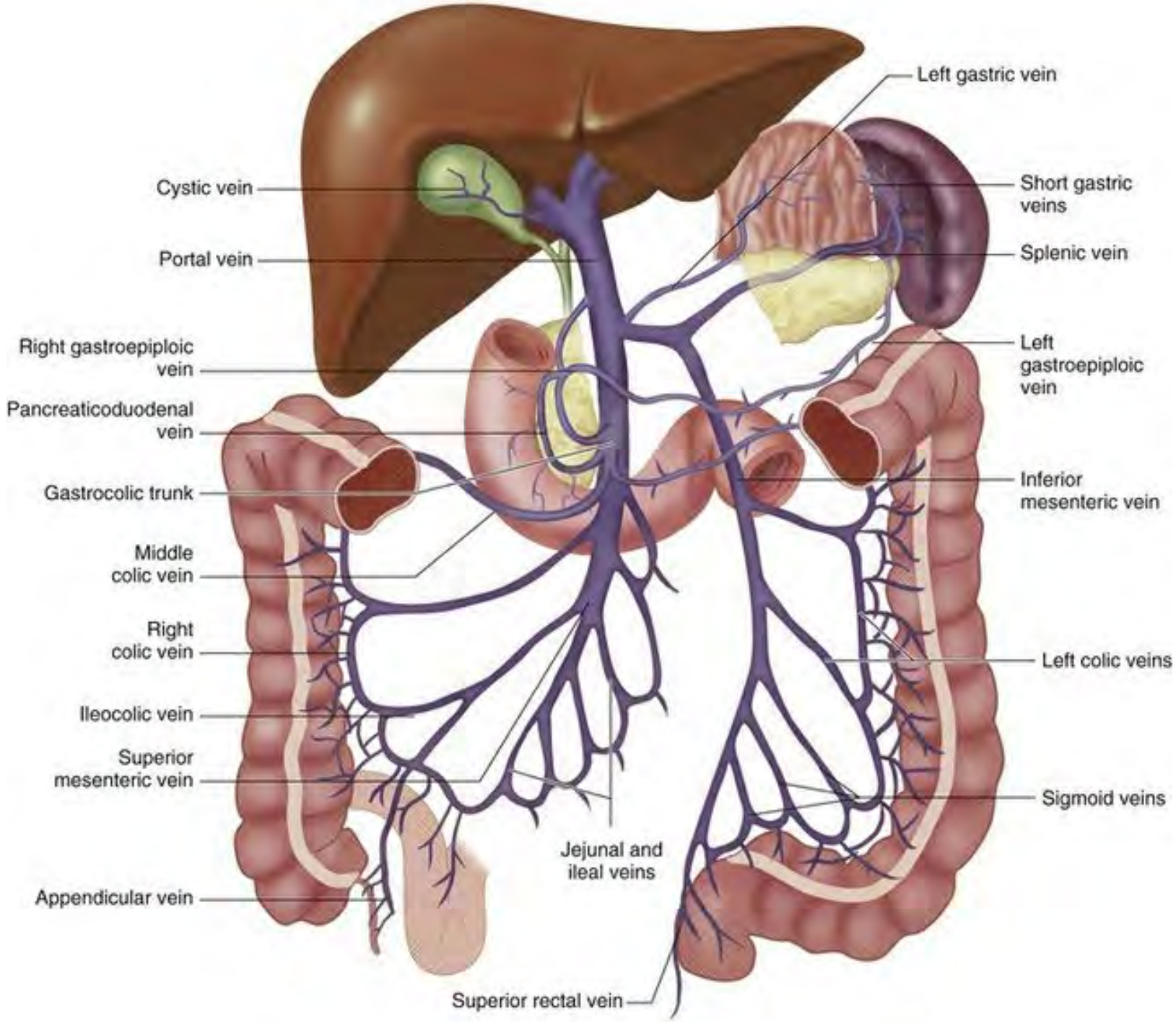

Common hepatic artery
R. gastric artery
L. hepatic artery
R. hepatic artery
Proper hepatic artery
Gastroduodenal artery
CA
L. gastric artery
Splenic artery
SMA
Middle colic artery
Arc of Riolan
Inf. pancreaticoduodenal artery
Right colic artery
Ileocolic artery
IMA
L. colic artery
Marginal artery of Drummond
Sigmoidal arteries
Superior rectal artery
© Mayo Clinic

Blood supply

- SMA (midgut) in between celiac trunk (foregut) and IMA (hindgut)
  - Watershed area splenic flexure (Griffith's point) between SMA/IMA
- Celiac trunk (T12)
  - Left gastric a (NB ulcers on lesser curve)
  - Splenic a (spleen, pancreas, fundus of stomach)
  - Hepatic a (gastroduodenal a with D1 ulcers)
  - Collaterals: pancreaticoduodenal arcades
  - Medial arcuate ligament syndrome
  - ~90° off aorta – low risk for embolism
- IMA (L3)
  - Left colic / sigmoid / sup rectal (watershed rectosigmoid (Sudeck point)
  - Collaterals: Marginal a of Drummond (SMA/IMA); Arc of Riolan (middle/Lt colic)
  - Vulnerable in AAA repair & Ao stents

Blood supply: SMA

- SMA (L1)
  - Inferior pancreaticoduodenal a: distal duodenum + pancreatic head
  - Jejunal & ileal branches
    - Jejunum fewer arcades & longer vasa recta
    - Ileum more arcades & shorter vasa recta
  - Ileocolic a: TI, cecum, appendix
  - Right colic a: ascending colon
  - Middle colic a: prox 2/3 TC (watershed with IMA at splenic flexure)
- ~ 38-65° off aorta
  - More prone to emboli with acute mesenteric ischaemia
  - Reduced fat pad makes angle more acute: Wilkie syndrome (<22°)
  - Nutcracker syndrome: left renal vv compressed between Ao & SMA


Left gastric vein
Cystic vein
Short gastric veins
Portal vein
Splenic vein
Right gastroepiploic vein
Left gastroepiploic vein
Pancreaticoduodenal vein
Gastrocolic trunk
Inferior mesenteric vein
Middle colic vein
Right colic vein
Left colic veins
Ileocolic vein
Superior mesenteric vein
Sigmoid veins
Jejunal and ileal veins
Appendicular vein
Superior rectal vein

Blood drainage

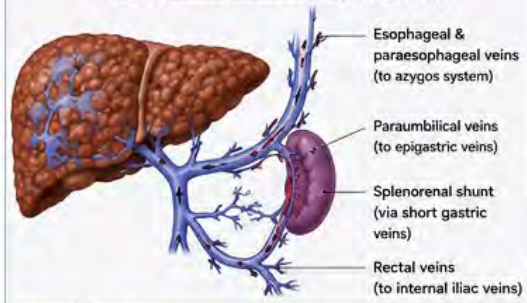
- SMV
  - Same name branches of aa drain to SMV
  - Union with splenic v & IMV to form PV infront of uncinate of pancreas
  - PV runs superiorly behind D1 in hepatoduodenal ligament to form porta hepatis with CBD and HA
- SMV thrombosis
  - Acute vs chronic ?isolated vs with PVT
  - Bowel wall oedema ±small intestine varices
  - Pain out proportion, diarrhoea/ileus, cx bowel ischaemia/infarction
  - Pneumatosis intestinalis

PORTAL HYPERTENSIVE SHUNTS – SPECIFIC SCENARIOS, EXPECTATIONS & THERAPEUTIC OPTIONS

Portal Hypertension = ↑ Resistance to portal blood flow → ↑ Portal venous pressure → Development of portosystemic collaterals (shunts)

1. CIRRHOSIS (SINUSOIDAL PORTAL HYPERTENSION)

Due to increased resistance in hepatic sinusoids

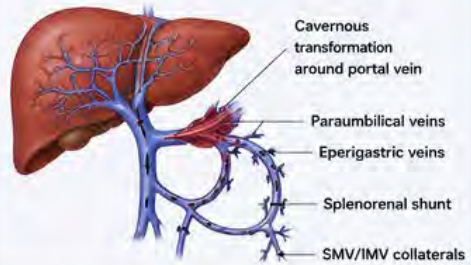


EXPECTATIONS

- Varices (esophageal, gastric, rectal)
- Ascites
- Splenomegaly, hypersplenism
- Hepatic encephalopathy

2. PORTAL VEIN THROMBOSIS (PVT)

Blockage of portal vein → pre-hepatic cause

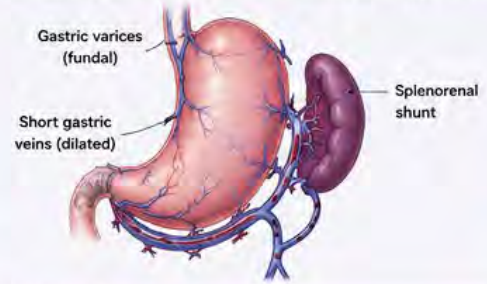


EXPECTATIONS

- Development of cavernous transformation
- Varices (similar to cirrhosis)
- Intestinal congestion (can cause bowel ischemia)
- Ascites (variable)

3. SPLENIC VEIN THROMBOSIS (SVT)

Blockage of splenic vein → isolated left-sided portal hypertension

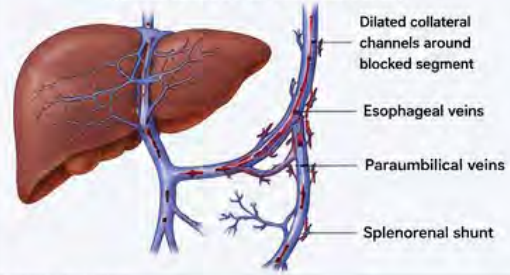


EXPECTATIONS

- Isolated gastric varices (fundal)
- Minimal/no esophageal varices
- No/less ascites
- Normal liver function (if liver not diseased)

4. SINASTRAL PORTAL HYPERTENSION

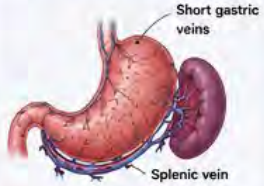
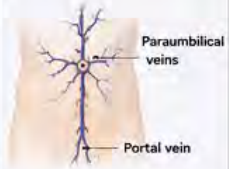
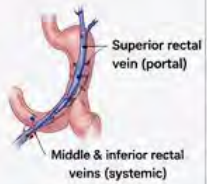
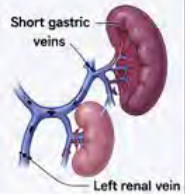
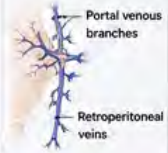
Pre-sinusoidal block in portal venous inflow
(Extrahepatic portal vein obstruction)



EXPECTATIONS

- Variceal bleeding (especially in children/young adults)
- Minimal hepatic dysfunction
- Hypersplenism

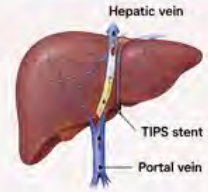
MAJOR PORTALSYSTEMIC SHUNTS – ANATOMY, DRAINAGE & CLINICAL SIGNIFICANCE

1. ESOPHAGEAL & PARAESOPHAGEAL	2. GASTRIC (FUNDAL)	3. PARAUMBILICAL	4. RECTAL	5. SPLENORENAL	6. MESENTERIC / RETROPERITONEAL
					
DRAINAGE Azygos / Hemiazygos vein (Systemic)	**DRAINAGE** Splenic vein → Left renal vein (Systemic)	**DRAINAGE** Epigastric veins → Superior/inferior epigastric veins (Systemic)	**DRAINAGE** Internal iliac veins (Systemic)	**DRAINAGE** Left renal vein (Systemic)	**DRAINAGE** Lumbar / diaphragmatic veins (Systemic)
SIGNIFICANCE Upper GI bleed (most common)	**SIGNIFICANCE** Fundal varices – risk of massive bleed (esp. in SVT)	**SIGNIFICANCE** Caput medusae	**SIGNIFICANCE** Hemorrhoids, rectal varices	**SIGNIFICANCE** Large shunt → high risk of hepatic encephalopathy	**SIGNIFICANCE** May cause chronic blood loss, ascites

THERAPEUTIC OPTIONS – KEY INTERVENTIONS

GENERAL MEASURES

- Non-selective beta blockers (↓ portal pressure)
- Endoscopic therapy (EVL / EIS)
- Treat underlying cause (cirrhosis, thrombosis, etc.)
- TIPS (refractory variceal bleed, refractory ascites)



BRTO / PARTO (For Gastric Varices)

- Balloon-occluded retrograde transvenous obliteration
- Preferred for fundal gastric varices with gastrorenal shunt
- Obliterates the shunt and varices without affecting portal inflow

SPLENECTOMY (Inflow Issue)

- Indicated for isolated splenic vein thrombosis with symptomatic hypersplenism or variceal bleed
- Removes main inflow (splenic) → reduces portal pressure on left side
- Improves cytopenias

SCENARIO-WISE SUMMARY: SHUNTS, EXPECTATIONS & MANAGEMENT PEARLS

SCENARIO	MAIN SHUNTS	EXPECTATIONS	KEY MANAGEMENT / OPTIONS
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SINASTRAL PORTAL HYPERTENSION	Esophageal, paraumbilical, splenorenal	Varices, hypersplenism, preserved liver function	Endotherapy, splenectomy (if hypersplenism), shunt surgery/TIPS (selected)

IMAGING POINTERS

- Doppler USG – evaluate portal vein patency, flow direction
- CT/MR venography – cavernous transformation, collaterals
- Look for: dilated veins at gastroesophageal junction, fundus, anterior abdominal wall, rectum, retroperitoneum

REMEMBER

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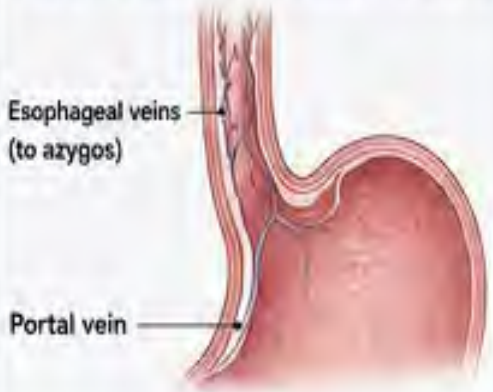	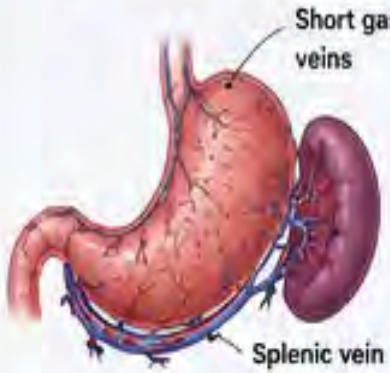	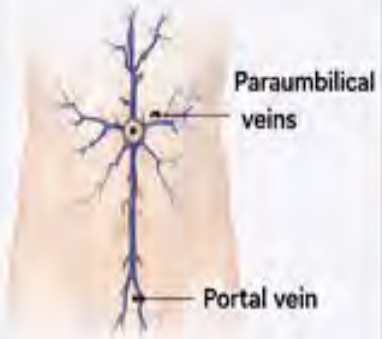	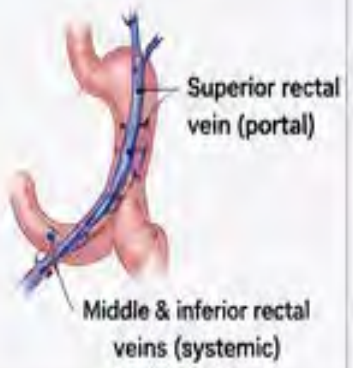		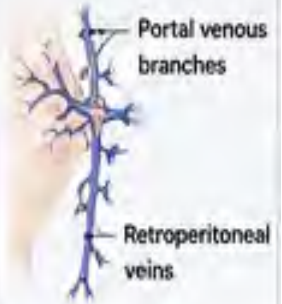
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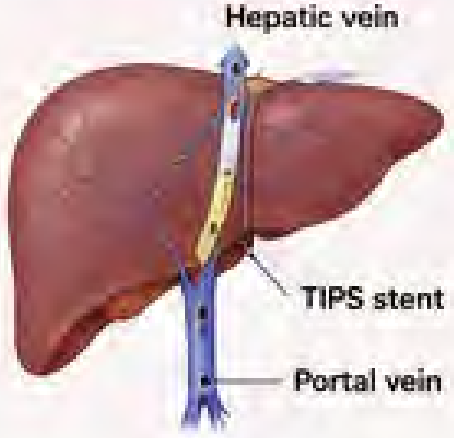

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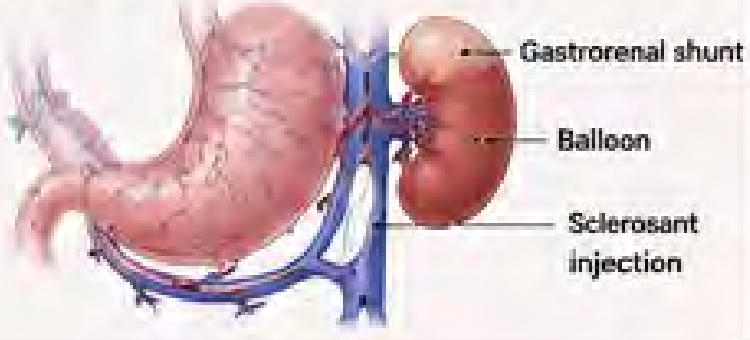

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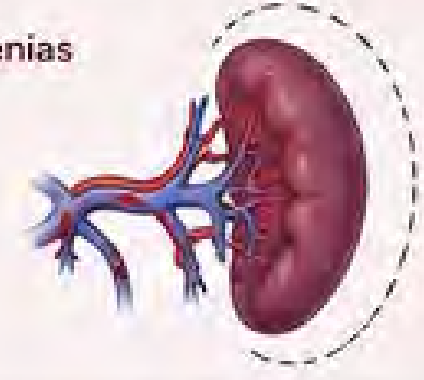

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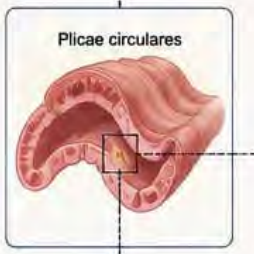
Lymphatics

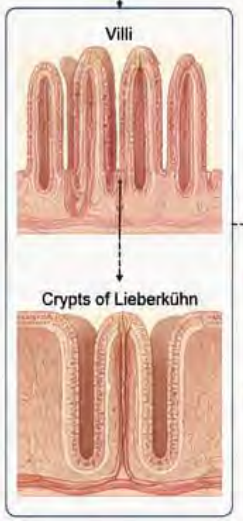
- For long chain trigs, cholesterol, phospholipids, fat soluble vitamins
- Mop up proteinaceous interstitial fluid from capillaries
- Flow rate – fasting 0.5-1l/d, normal diet 2l/d, fatty 4-6l/d, cirrhosis ~20l/d
- Lacteals to submucosal lymphatics
- Mesenteric lymphatics
- Mesenteric LN (essentially similar to vascular anatomy ie jejunal, ileal and superior mesenteric LN)
- Cisterna chyli
  - L1/L2 behind rt crus of diaphragm
  - Reservoir where lipid rich chyle from intestinal & lumbar trunks converge
- Thoracic duct runs in posterior mediastinum
- Lt venous angle at junction of Lt internal jug & subclavian vein

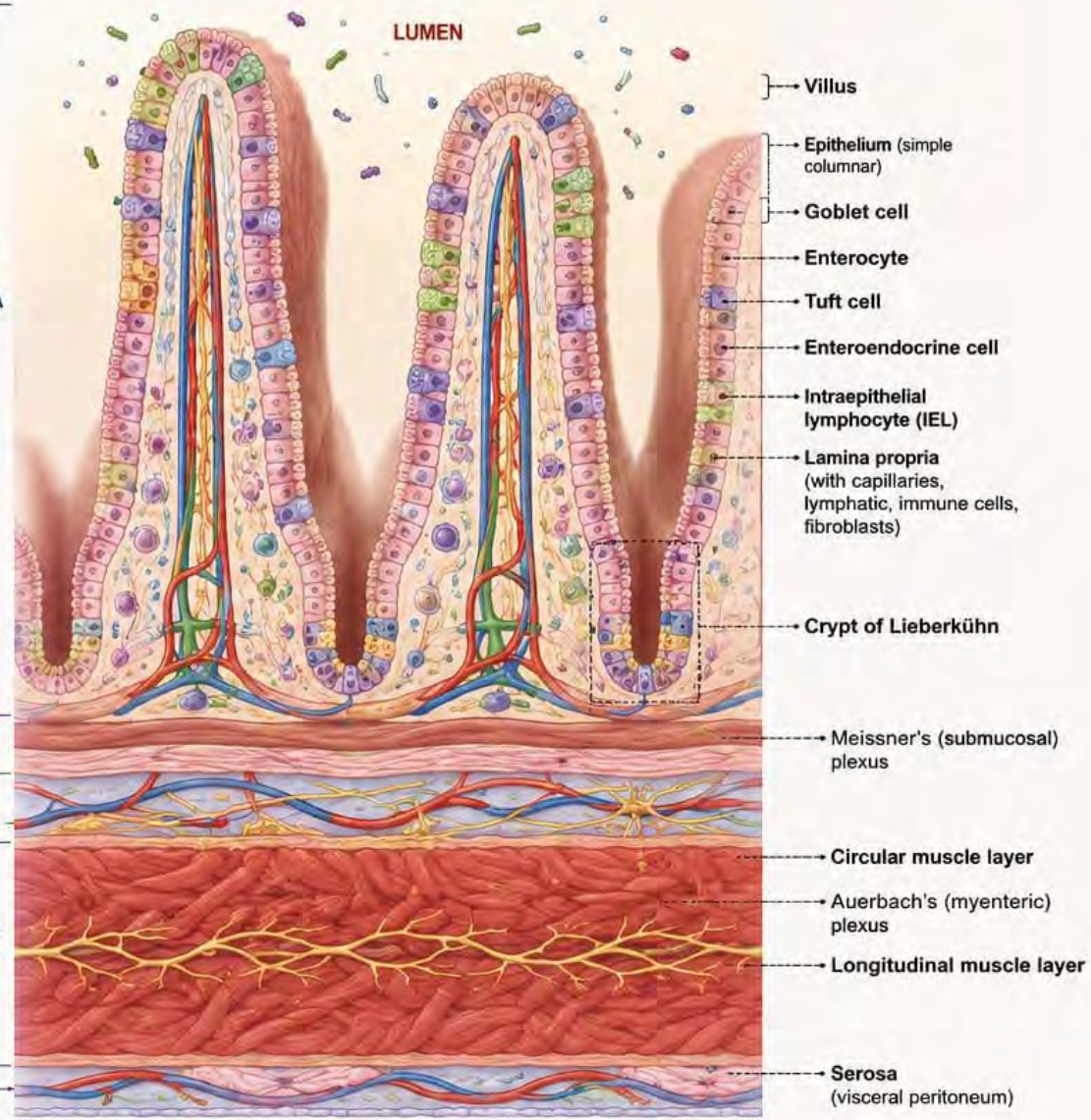
Mesentery

- Double fold peritoneum that suspends all small bowel
- Encompasses mesenteric vessels & lymphatics
- 15cm root from Lt L2 transverse process to Rt sacroiliac joint
- 4-6m fan
- More than just a support structure
  - Immune hub (relevance in anti-mesenteric surgery in Crohn's)
  - Fat/lipid metabolism
    - Adiponectin, leptin, resistin, omentin, gherlin
  - Tissue repair
- Sclerosing mesenteritis

SMALL BOWEL MICROANATOMY







MUCOSAL EPITHELIAL CELLS

Enterocyte
Absorptive cell with brush border (microvilli); nutrient and fluid absorption

Goblet cell
Secretes mucus for lubrication and protection

Tuft cell
Chemosensory cell; detects luminal signals (bitter compounds, succinate); releases IL-25, eicosanoids

Enteroendocrine cell
Secretes hormones (e.g., CCK, GLP-1, secretin, GIP, serotonin) to regulate digestion and motility

Paneth cell (in crypts)
Secretes antimicrobial peptides (lysozyme, defensins) and supports stem cells

Stem cell (in crypt base)
Lgr5+ stem cell that proliferates to renew epithelium

IMMUNE CELLS

IEL (Intraepithelial lymphocyte)
T cells located between epithelial cells; immune surveillance

LPMC (Lamina Propria Mononuclear Cell)
B cells, T cells, plasma cells, macrophages, dendritic cells in lamina propria

KEY FEATURES

Villi increase surface area for absorption.

Crypts of Lieberkühn contain stem cells and Paneth cells; driving epithelial renewal and defense.

Mucus (from goblet cells) forms a protective barrier.

Enteric nervous system (Meissner's & Auerbach's plexuses) regulates secretion, blood flow, and motility.

Rich blood supply and lymphatics in lamina propria support absorption and immunity.

Brush border enzymes (on enterocytes) complete digestion of nutrients.

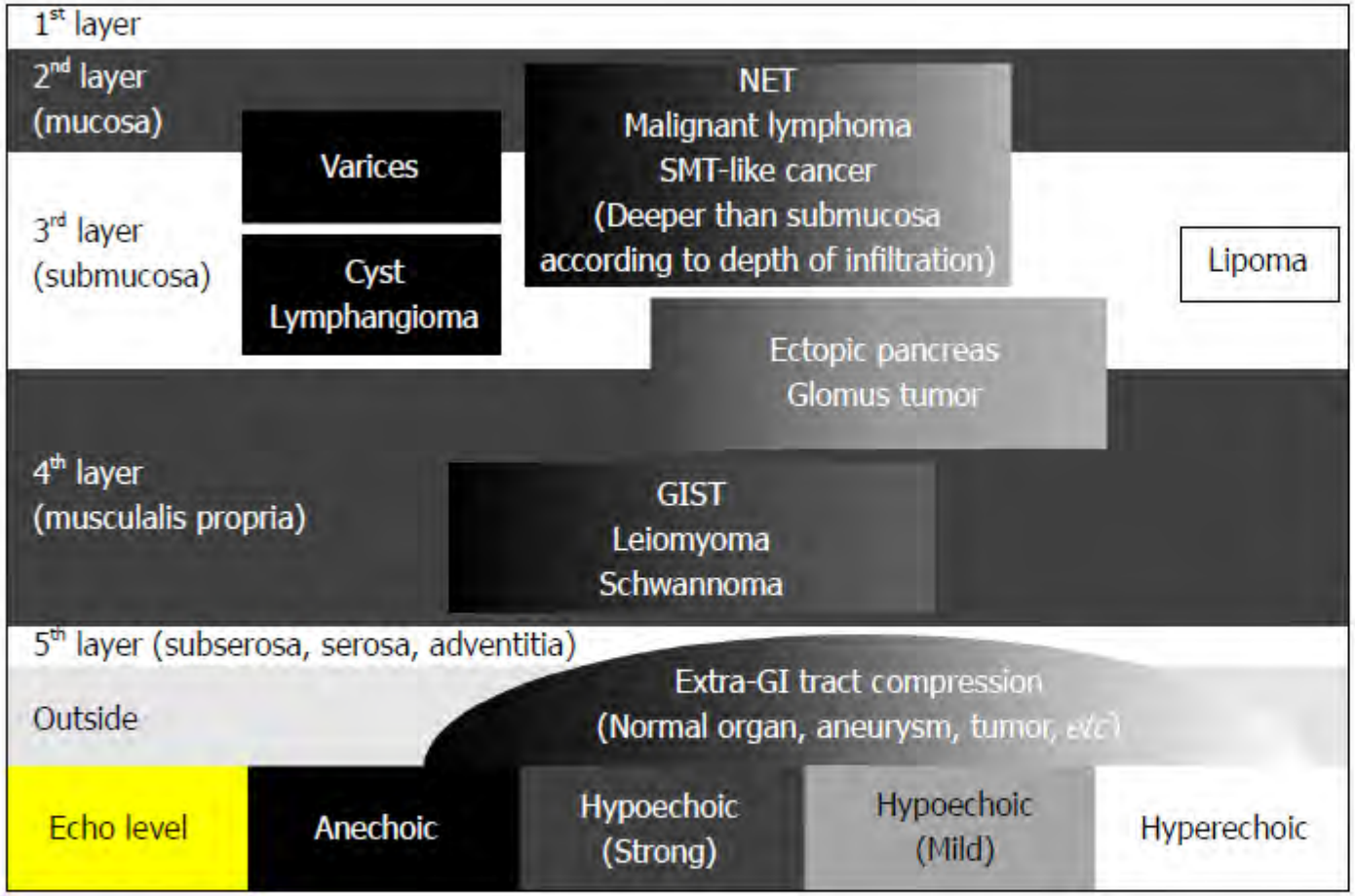
LAYER SUMMARY

Mucosa
Epithelium + lamina propria + muscularis mucosae

Submucosa
Connective tissue, vessels, nerves (Meissner's plexus)

Muscularis externa
Circular muscle + Auerbach's plexus + Longitudinal muscle

Serosa
Outer protective layer (visceral peritoneum)



Endoscopic ultrasound
Alternating
hypo/hyperechoic
layers of intestinal wall

Figure 4 Differential diagnosis of subepithelial lesions by endoscopic ultrasound. Quoted and modified from reference[39] with permission. GIST: Gastrointestinal stromal tumor.

Akahoshi et al., Current clinical management of gastrointestinal stromal tumor, World J Gastroenterol 2018 July 14; 24(26): 2806-281

Microscopic anatomy

1) Mucosa
   - Simple columnar epithelium enterocytes with microvilli brush border & glycocalyx
   - Mucus producing goblet cells (Trefoil factors)
   - Crypts of Lieberkuhn: Paneth cells/stem cells/enteroendocrine cells
   - Tuft cells – important role in helminths, Th2 response pathway
   - Taste receptors: sweet, bitter, umami and fat
   - Lamina propria: blood capillaries & lacteals
   - Muscularis mucosae: thin smooth muscle layer separating from submucosa
2) Submucosa
   - Thick connective tissue layer housing larger vessels, lymphatics & **Meissner's plexus**
3) Muscularis propria
   - Two smooth muscle layers sandwiching the **Auerbach's plexus**
4) Serosa
   - Mesothelial cell covered connective tissue layer
   - Adventitia for retroperitoneal sections (prox duodenum)

Trefoil factors

- Three-loop peptide molecules secreted by goblet cells
- Role in epithelial healing, mucus viscosity, innate immune system
- TFF1
  - Mainly gastric, tumour suppressive like peptide
  - Reduced in H Pylori, CAG/IM
  - Loss associated with gastritis, ulcers, adenoca
- TFF2
  - Stomach & Brunner’s glands: spasmolytic polypeptide
  - Spasmolytic polypeptide-expressing metaplasia (SPEM)
- TFF3
  - Small intestine & colon: co-secreted with MUC2 mucin into glycocalyx
  - Epithelial restitution, tight-junctions, microbiota & innate immunity crosstalk
  - Stimulated with TLR2; inhibited by TNF alpha/NF-KB
  - Reduced expression in IBD (Potential therapeutic target incl radiation/chemo)

Glycocalyx

- Carbohydrate rich layer covering microvilli of enterocytes
- Important in barrier integrity, host-microbiome interaction, immune signalling, nutrient digestion & absorption
- Enzymes: disaccharidases & peptidases
- Vulnerable to
  - Acute (viral enteritis, bacterial toxins)
  - Chronic (Crohn's, Celiac, GVHD, radiation enteritis, SIBO)
  - Ischaemia
  - Hyperglycaemia
  - Drugs (NSAIDS/chemo/Alcohol/broad spectrum antibiotics)
  - Environmental/tropical enteropathy (poor sanitation, recurrent enteritis)
  - Prolonged TPN (luminal nutrition tropic to enterocytes (SCFA - butyrate))
- Results in
  - "leaky gut", malabsorption ~ PLE
  - Osmotic diarrhoea (carb/lactose) / post prandial bloating
  - Increased bacterial translocation
  - Gut-liver axis

Microbiome & immunogenics

- High antigenic load in gut (bacteria, food) & requires tolerogenicity
  - SIgA, mucin, defensins, decreased TLR expression
- GALT, IEL, LPMC
  - “physiological inflammation”
- Microbiome & host interplay
  - Less abundance & diversity compared to colon (too much – SIBO)
  - Important in SFCA production, Tregs
  - Gut-liver-brain axis
  - Influence GLP-1, bile acid metabolism, serotonin pathways
  - OmpC, CBir1 (bacteria), NOD2, CARD9 (host)
- A

Neural innervation

- Enteric nervous system (ENS)
  - Meissner plexus: secretion
    - Secretory diarrhoea, bacterial translocation
  - Myenteric (Auerbach) plexus: peristalsis
    - Migrating motor complex: fasting, phase I-III
    - Dysmotility/ileus/pseudo-obstruction/bloating/SIBO
  - Interstitial cells of Cajal
    - pacemaker cells coordinating slow waves & peristalsis
  - Excitatory (Ach, substance P) & inhibitory (NO, VIP) neurotransmitters
- Autonomic nervous system
  - Parasympathetic from vagus
  - Sympathetic from celiac & SMA
- Afferent
  - Detects distension, osmolarity, inflammation
  - Hypersensitisation: visceral hypersensitivity with functional abdominal sx, IBS

MAJOR MOTOR COMPLEX (MMC): PHASES 1–3

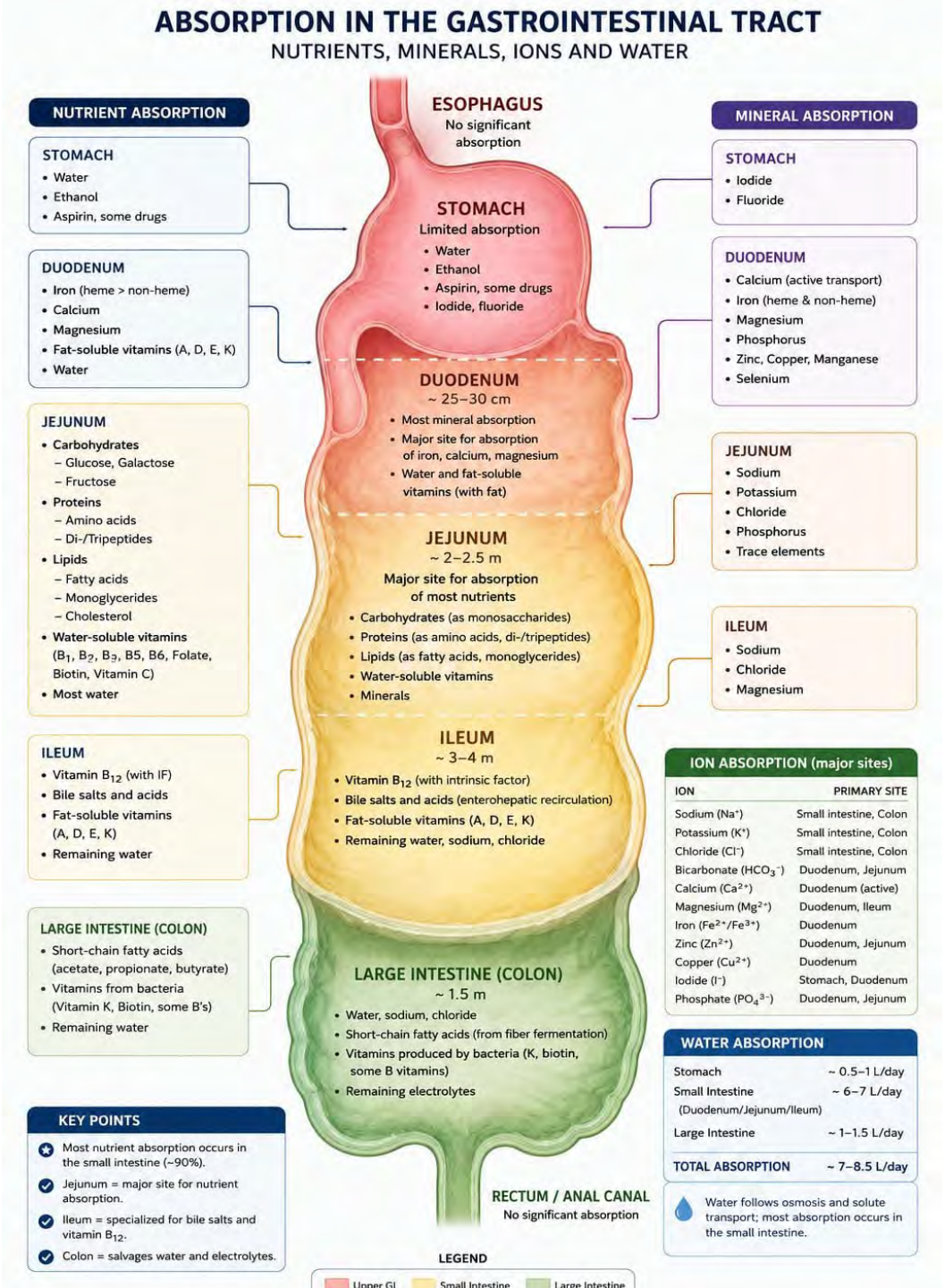
FEATURE	PHASE 1 (QUIESCENT)	PHASE 2 (IRREGULAR ACTIVITY)	PHASE 3 (PROPULSIVE ACTIVITY)	STIMULI (↑) & INHIBITORS (↓) INCLUDING MEDICATIONS
DURATION	40–60 min (about 45–60%)	20–40 min (about 30–40%)	5–10 min (about 5–10%)	**STIMULI (↑)** • Fasting state • Parasympathetic activity (Vagus nerve) • Motilin – **Drugs:** Erythromycin* (binds to motilin receptor and acts as agonist)
MOTOR PATTERN	No contractions ("resting phase")	Irregular, intermittent contractions	Regular, strong contractions that migrate aborally	
PHYSIOLOGIC ROLE	• Fasting baseline • Allows digestion & absorption to complete	• Intervening activity • Gradual increase in activity before phase 3	• "Housekeeper wave" • Sweeps residual food, mucus, bacteria proximally ⟶ distally • Clears small intestine	
STIMULI (What starts/ strengthens it)	• Fasting state • Vagal (parasympathetic) activity • Cycle recurs every 90–120 min	Transition phase – no specific stimulus; represents gradual build-up of activity	STRENGTHENED BY: • Fasting • Parasympathetic (ACh, GRP+) • Motilin (from M cells of duodenum & jejunum – cyclic release)	**INHIBITORS (↓) & MEDICATIONS** • Food (distension) & nutrients (fat, protein, hyperosmolar) • Hormones: – Secretin, CCK, GIP, GLP-1, PYY • Sympathetic activity (NE) • **Medications that inhibit MMC:** – **Opioids:** morphine, codeine – **Anticholinergics:** atropine, hyoscine (scopolamine) – **Octreotide** (somatostatin analog) – **Proton pump inhibitors** (indirectly via ↑ gastric pH/food retention) – **Benzodiazepines, tricyclic antidepressants** (↓ motility)
INHIBITORS (↓ MMC)	• Eating (stomach/duodenal distension) • Presence of nutrients (esp. fat, protein, hyperosmolar solutions) • Stress, pain • Sympathetic activity (NE) • Secretin, CCK, GIP, GLP-1, PYY (all inhibit MMC)	• Eating (stomach/duodenal distension) • Presence of nutrients (esp. fat, protein, hyperosmolar solutions) • Stress, pain • Sympathetic activity (NE) • Secretin, CCK, GIP, GLP-1, PYY (all inhibit MMC)	• Eating (stomach/duodenal distension) • Presence of nutrients (esp. fat, protein, hyperosmolar solutions) • Stress, pain • Sympathetic activity (NE) • Secretin, CCK, GIP, GLP-1, PYY (all inhibit MMC)	
KEY MEDICATIONS THAT INCREASE MMC	—	—	**Prokinetics / Motilin receptor agonists:** • **Erythromycin*** (binds to motilin receptor) • **Metoclopramide** (↑ ACh release; prokinetic) • **Domperidone** (D_2 antagonist; prokinetic)	
SEQUENCE	Occurs every 90–120 minutes during fasting Phase 1 40–60 min (Quiescent) → Phase 2 20–40 min (Irregular activity) → Phase 3 5–10 min (Propulsive activity) - - -→ Phase 1 (Next cycle)			

* Erythromycin is an antibiotic that acts as a motilin receptor agonist at low (prokinetic) doses to stimulate MMC.

Abbreviations: ACh = acetylcholine; GRP = gastrin-releasing peptide; NE = norepinephrine; CCK = cholecystokinin; GIP = glucose-dependent insulinotropic peptide; GLP-1 = glucagon-like peptide-1; PYY = peptide YY.

Simplified overview

- Duodenum
  - Brunner’s glands – bicarb
  - Ampulla of Vater
  - Iron, ions & metal absorption
  - Gastric emptying regulator
- Jejunum
  - Long and “leaky” – fluid absorption
- Ileum
  - Peyer’s patches
  - B12 and bile salt absorption



Duodenum

- 25-30cm
- D1: superior/bulb (5cm)
  - Connected to undersurface of liver (porta hepatitis) by hepatoduodenal ligament
  - Gastroduodenal aa (risk in duodenal bulb ulcers)
- D2: descending/ C loop (10cm)
  - Major & minor duodenal papilla
  - Head of pancreas lies in concavity of duodenal C
- D3: horizontal (7.5cm)
  - Runs Rt->Lt with IVC & aorta behind
  - SMV & SMA infront (Wilke syndrome)
- D4: ascending (2.5cm)
  - Duodenojejunal flexure supported by ligament of Treitz (demarcation of upper GI) at L2

Duodenum – digestion

- Receives
  - Acidic chyme from stomach
  - Ampulla of vater – CBD
    - Pancreatic duct
      - Bicarb rich fluid: neutralise acidic chyle & facilitate pancreatic enzyme fx
      - Protein enzymes: trypsinogen/chymotrypsinogen/proelastase/procarboxypetidase
      - Lipid enzymes: pancreatic lipase
      - Carbohydrate: amylase
    - Cystic duct: bile salts, phospholipids, bicarb, bilirubin (emulsifies fats, forms micelles)
- Brush border
  - Contains
    - Protein ezymes: aminopeptidases, carboxy/dipeptidase
    - Fat enzymes: phosphatases/esterases, ALP (detoxifies LPS)
    - Carbohydrate: maltase, sucrase, lactase, disaccharidase
    - Dctyb (Fe^{3+} -> Fe^{2+})
  - Enteropeptidase to activate trypsin which in turns activates other enzymes

Gastrointestinal peptide families

Family	Members
Gastrin-cholecystokinin family	Gastrin
	Cholecystokinin
Secretin-glucagon family	Secretin
	Glucagon
	Vasoactive intestinal polypeptide
	Glucagon-like peptides (GLP-1 and GLP-2)
	Peptide histidine-isoleucine (PHI)
	Glucose-dependent insulinotropic polypeptide (also called gastric inhibitory polypeptide)
	Pituitary adenylate cyclase-activating polypeptide (PACAP)
Pancreatic polypeptide family	Pancreatic polypeptide (PP)
	Neuropeptide Y (NPY)
	Peptide YY (PYY)
Tachykinin family	Substance P
	Substance K
Bombesin family	Neuromedin B
	Gastrin-releasing polypeptide (GRP)
Opioid family	Enkephalin
	Beta-endorphin
	Dynorphin
	Adrenocorticotropic hormone
	Alpha-melanocyte stimulating hormone
Growth factors	Epidermal growth factor
	Transforming growth factor (TGF-alpha, TGF-beta)
	Insulin-like growth factor
Other peptides	Somatostatin
	Motilin
	Neurotensin
	Galanin
	Endothelin

LIVER, GALLBLADDER & PANCREAS: DUCTS, DRAINAGE AND HORMONAL CONTROL

LIVER

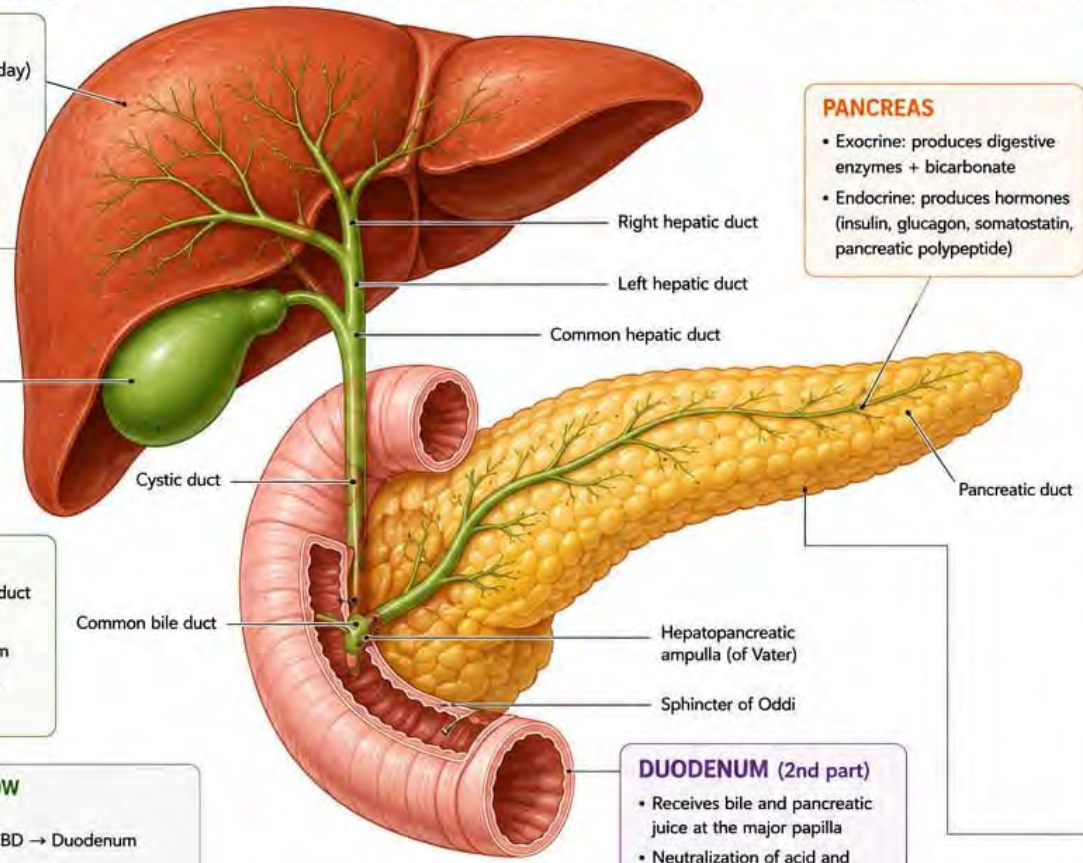
- Produces bile (800–1000 mL/day)
- Bile is made of bile salts, cholesterol, phospholipids, bilirubin, electrolytes
- Bile aids in fat digestion and absorption

GALLBLADDER

- Stores and concentrates bile (30–60 mL capacity)
- Releases bile in response to CCK

BILIARY DUCTS

- Cystic duct + Common hepatic duct → Common bile duct (CBD)
- CBD transports bile to duodenum
- Sphincter of Oddi regulates flow into duodenum



PANCREAS

- Exocrine: produces digestive enzymes + bicarbonate
- Endocrine: produces hormones (insulin, glucagon, somatostatin, pancreatic polypeptide)

DUODENUM (2nd part)

- Receives bile and pancreatic juice at the major papilla
- Neutralization of acid and digestion of fats, proteins and carbohydrates

DUCTAL FLOW

- **Bile flow**
  Liver → Hepatic ducts → CBD → Duodenum
- **Pancreatic juice flow**
  Pancreas → Pancreatic duct → Duodenum
- **Mixed flow at ampulla**
  Bile + Pancreatic juice → Duodenum

KEY POINTS

- ✓ Bile emulsifies fats; pancreatic enzymes digest carbs, proteins, fats.
- ✓ Bicarbonate neutralizes acid and provides optimal pH for enzymes.
- ✓ Ducts converge at the hepatopancreatic ampulla and are regulated by the sphincter of Oddi.
- ✓ Hormones and enteric signals coordinate bile and pancreatic secretion with intestinal digestion.

COORDINATED DIGESTIVE RESPONSE

(Synergistic control for optimal digestion)

- Acidic fat-rich chyme enters duodenum
  ↓
  Secretin → ↑ Bicarbonate-rich fluid (pancreas & liver)
  CCK → ↑ Enzyme-rich secretion (pancreas) + Gallbladder contraction
  VIP → Relax sphincter of Oddi & intestinal smooth muscle
  GIP/GLP-1 → Enhance insulin release & nutrient handling

Result: Neutral pH, enzyme delivery, bile release, and efficient digestion & absorption

KEY HORMONES: SOURCES, STIMULI, TARGETS & ACTIONS

1) CCK (Cholecystokinin)

STIMULUS (from intestine)	RELEASED BY	ACTIONS / TARGETS
• Fatty acids, monoglycerides • Amino acids, peptides	I-cells in duodenum and jejunum	• Gallbladder contraction • Relaxation of sphincter of Oddi • ↑ Pancreatic acinar enzyme secretion • Trophic effect on pancreas

2) SECRETIN

STIMULUS (from intestine)	RELEASED BY	ACTIONS / TARGETS
• Acidic chyme (low pH) in duodenum	S-cells in duodenum	• ↑ Pancreatic ductal bicarbonate and fluid secretion • ↑ Bile flow (bicarbonate-rich, water-rich bile from liver) • Inhibits gastric acid secretion

3) VIP (Vasoactive Intestinal Peptide)

STIMULUS (from intestine)	RELEASED BY	ACTIONS / TARGETS
• Fat, acid, or distension (via enteric reflexes)	Enteric neurons (non-adrenergic, non-cholinergic) and some I-cells	• Relaxation of smooth muscle: – Sphincter of Oddi – Intestinal wall • ↑ Pancreatic and biliary bicarbonate secretion • ↑ Intestinal blood flow

4) GIP (Glucose-dependent Insulinotropic Peptide)

STIMULUS (from intestine)	RELEASED BY	ACTIONS / TARGETS
• Glucose, fatty acids, oral nutrients (mainly in duodenum and jejunum)	K-cells in duodenum and jejunum	• ↑ Insulin secretion (glucose-dependent) • Inhibits gastric acid secretion • May ↑ lipid storage

5) GLP-1 (Glucagon-like Peptide-1)

STIMULUS (from intestine)	RELEASED BY	ACTIONS / TARGETS
• Nutrients: carbohydrates, fats, proteins (mainly in ileum and colon but also in jejunum)	L-cells in ileum and colon (also jejunum)	• ↑ Insulin secretion (glucose-dependent) • ↓ Glucagon secretion • Slows gastric emptying • Promotes satiety

SUMMARY: MAIN EFFECTS ON LIVER, GALLBLADDER & PANCREAS

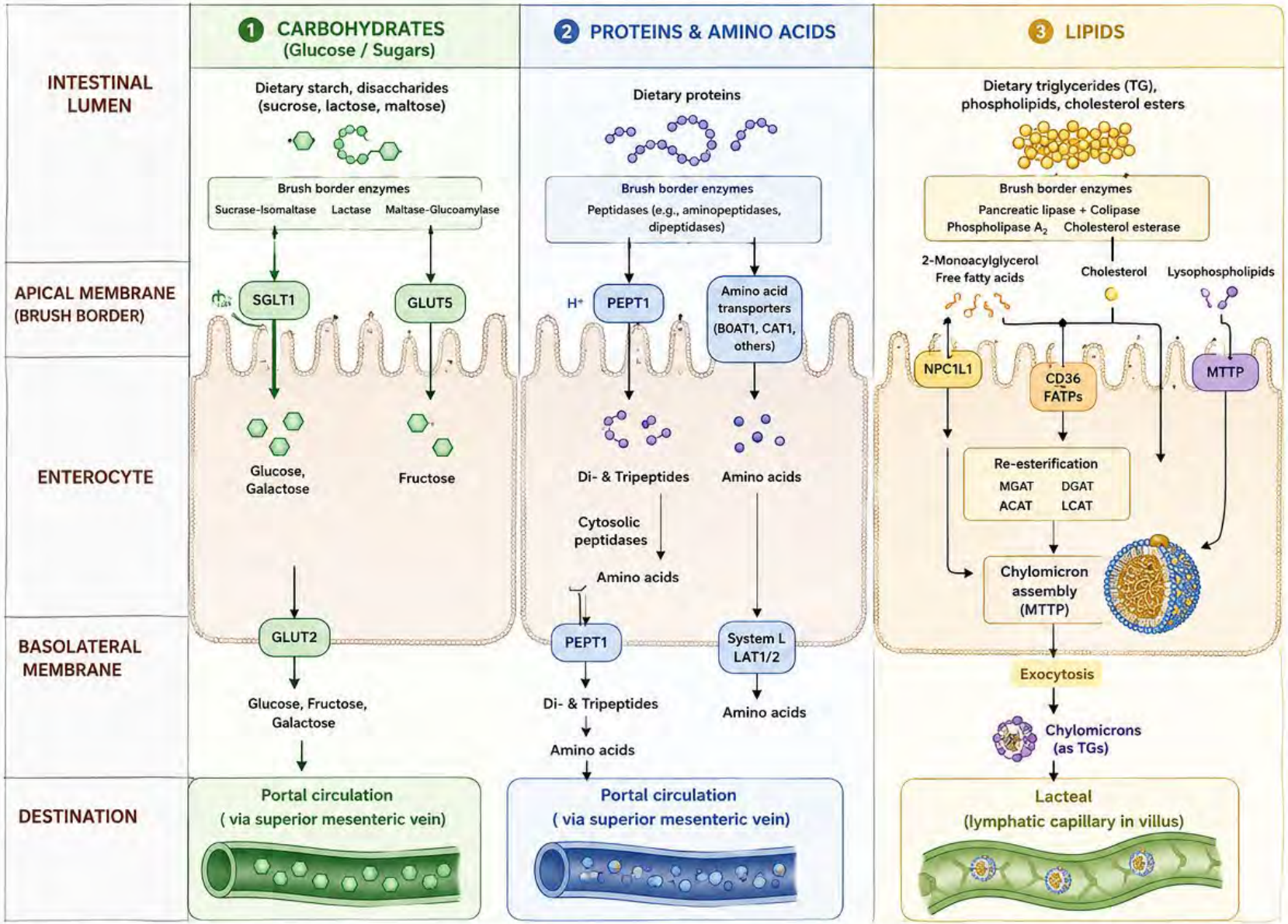
Hormone	Gallbladder	Sphincter of Oddi	Pancreatic Acinar	Pancreatic Ductal (HCO_3^-)	Bile Flow	Gastric Acid Secretion	Insulin Release
CCK	Contraction	Relaxation	↑ Enzymes	–	–	–	– (indirect)
Secretin	–	(mild relax)	–	↑ HCO_3^- + Fluid	↑ (bile flow)	↓ Inhibits	–
VIP	–	Relaxation	–	↑ HCO_3^- + Fluid	↑	↓	–
GIP	–	–	–	–	–	↓ Inhibits	↑ (glucose-dependent)
GLP-1	–	–	–	–	–	(slows emptying)	↑ (glucose-dependent)

Abbreviations: CCK = Cholecystokinin, VIP = Vasoactive Intestinal Peptide, GIP = Glucose-dependent Insulinotropic Peptide, GLP-1 = Glucagon-like Peptide-1

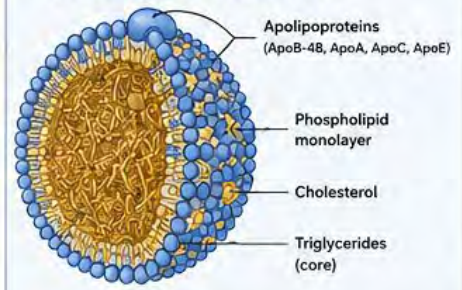
- CCK (I cells)
  - Stimulated by fats, proteins > carbs.
  - GB contraction, sphincter of Oddi relaxation, pancreatic enzyme secretion, tLESRs (CCK1)
  - Inhibits gastric motility & promotes acid production (CCK2/gastrin R). Induces satiety & augment incretins
  - CCKoma (rare): elevated CCK without gastrin; diarrhoea, wt loss, gallstones & PUD
- Secretin (S cells)
  - Stimulated by acidic pH/luminal H+
  - Stimulates pancreatic fluid & bicarb secretion to neutralise gastric acid. Brunner glands buffer secretion
  - Inhibits gastric motility & acid production. Induces satiety
  - Secretin stim test: paradoxical gastrin increase in gastrinoma
- GIP (K cells)
  - Incretin, stimulate glucagon during eu/hypoglycaemia, storage for fat
- GLP1/GLP2/PYY (L cells)
  - Part of the ileal break – fat>protein in ileum negative feedback on motility/gastric acid
  - GLP1: incretin, gastric slowing, also mediated bile salts via TGPR5, vagal stimulation
  - GLP:2 gut trophic hormone (Tedaglutide)
  - PYY: most important cog in inhibiting gastric motility & acid secretion
- VIP
  - Stimulated by luminal distension
  - Potent vasodilator for nutrient absorption, water & Cl- secretion & smooth muscle relaxation
  - Various endocrine effects (adrenal, pancreas, hypothalamus/pituatiry, thyroid)
  - Immunomodulatory (Th2>Th1, inhibits interferon gamma, IL-2, TNF alpha)
  - VIPoma: WDHA / Verner-Morrison syndrome
- Motilin (M cells)

NUTRIENT ABSORPTION IN THE SMALL INTESTINE

Pathways, Transporters, Enzymes & Destinations



CHYLOMICRON STRUCTURE



KEY TRANSPORTERS (Apical)

- **SGLT1** : Glucose/galactose + Na^+ cotransporter
- **GLUT5** : Fructose transporter
- **PEPT1** : H^+ -peptide cotransporter
- **Amino acid transporters** : Na^+ -independent uptake
- **NPC1L1** : Cholesterol transporter
- **CD36 / FATPs** : Long-chain fatty acid transporters
- **MTTP** : Microsomal triglyceride transfer protein (chylomicron assembly)

KEY ENZYMES

- **Carbohydrates** : Sucrase-Isomaltase, Lactase, Maltase-Glucoamylase
- **Proteins** : Peptidases (aminopeptidases, dipeptidases), Cytosolic peptidases
- **Lipids** : Pancreatic lipase, Colipase, Phospholipase A_2, Cholesterol esterase; MGAT, DGAT, ACAT, LCAT

KEY POINTS

- ✓ Glucose & amino acids → absorbed directly into portal blood.
- ✓ Lipids → re-esterified and packaged into chylomicrons → enter lymph via lacteals.
- ✓ Enterocytes coordinate digestion, absorption and nutrient delivery efficiently.

SGLT1 – Sodium-glucose cotransporter 1 | GLUT2/5 – Glucose transporters | PEPT1 – Peptide transporter 1 | FATP – Fatty acid transport protein
NPC1L1 – Niemann-Pick C1-Like 1 | MTTP – Microsomal triglyceride transfer protein | MGAT – Monoacylglycerol acyltransferase
DGAT – Diacylglycerol acyltransferase | ACAT – Acyl-CoA cholesterol acyltransferase | LCAT – Lecithin cholesterol acyltransferase

Lipid absorption

- P-lipase hydrolyses
- Bile salts emulsify -> Micelles (LCT, cholesterol, ADEK)
- MCT – absorption via portal vein system
- Enterocyte – apolipoproteins to form chylomicrons
- Lacteals -> mesenteric lymphatics -> mesenteric LN -> cisterna chyli (Rt crus of diaphragm) -> thoracic duct -> Lt venous angle

Chylous ascites
Aim to reduce lymph flow
Hence low fat, MCT diet -> fasting with TPN
Somatostatin analogues

1 Lumen: Emulsification & Enzymatic Digestion

- Bile salts emulsify dietary fats.
- Pancreatic lipase hydrolyzes triglycerides (TG) to free fatty acids (FFA) and monoglycerides.

2 Enterocyte Uptake

- FFA and monoglycerides form micelles with bile salts.
- Micelles deliver lipids to the enterocyte where they diffuse across and are absorbed.

3 Re-esterification & Chylomicron Formation

- Inside the enterocyte, FFA are re-esterified to triglycerides.
- Triglycerides, cholesterol, and proteins assemble with ApoB-48 to form chylomicrons.

4 Lymphatic Transport

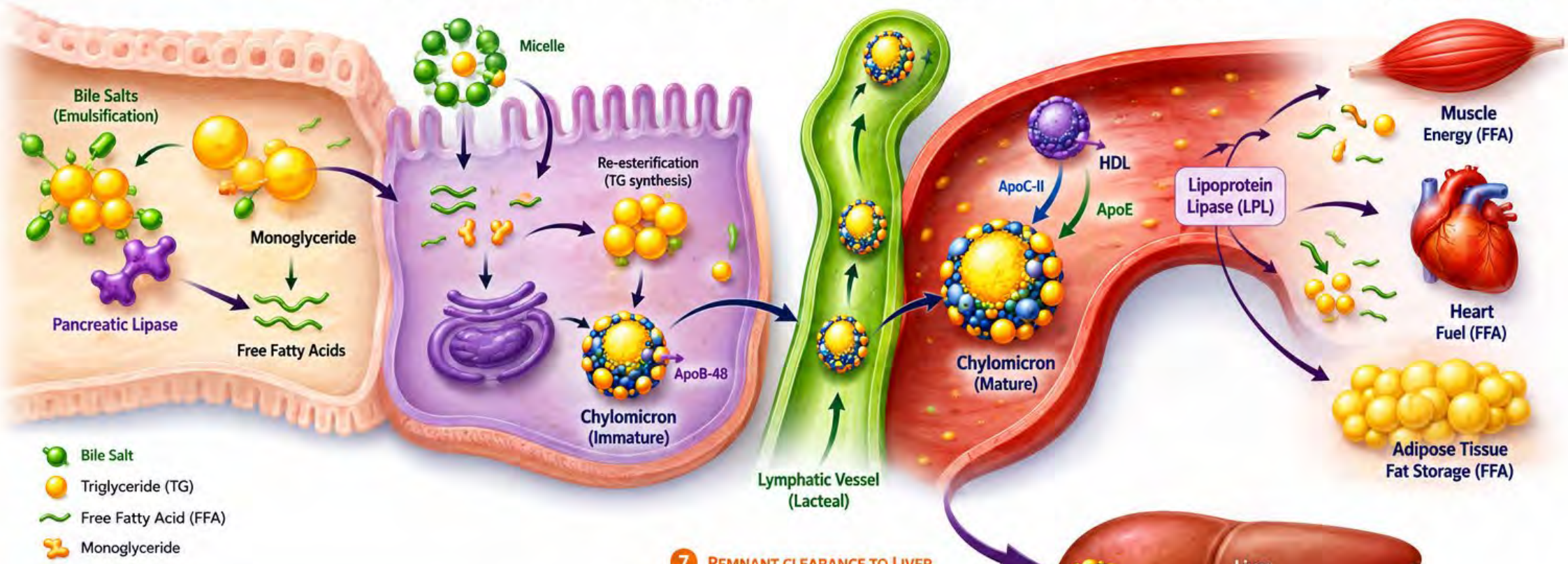
- Chylomicrons are exocytosed into the lymphatic lacteals.
- They travel via lymph to the thoracic duct and enter the bloodstream.

5 Maturation in Blood: HDL & Apolipoproteins

- In blood, chylomicrons acquire ApoC-II and ApoE from HDL.
- ApoC-II activates lipoprotein lipase (LPL); ApoE mediates remnant clearance.

6 Lipid Delivery to Tissues

- LPL (activated by ApoC-II) hydrolyzes TG → FFA.
- FFA are taken up by muscle and heart for energy or by adipose tissue for storage.



7 Remnant Clearance to Liver

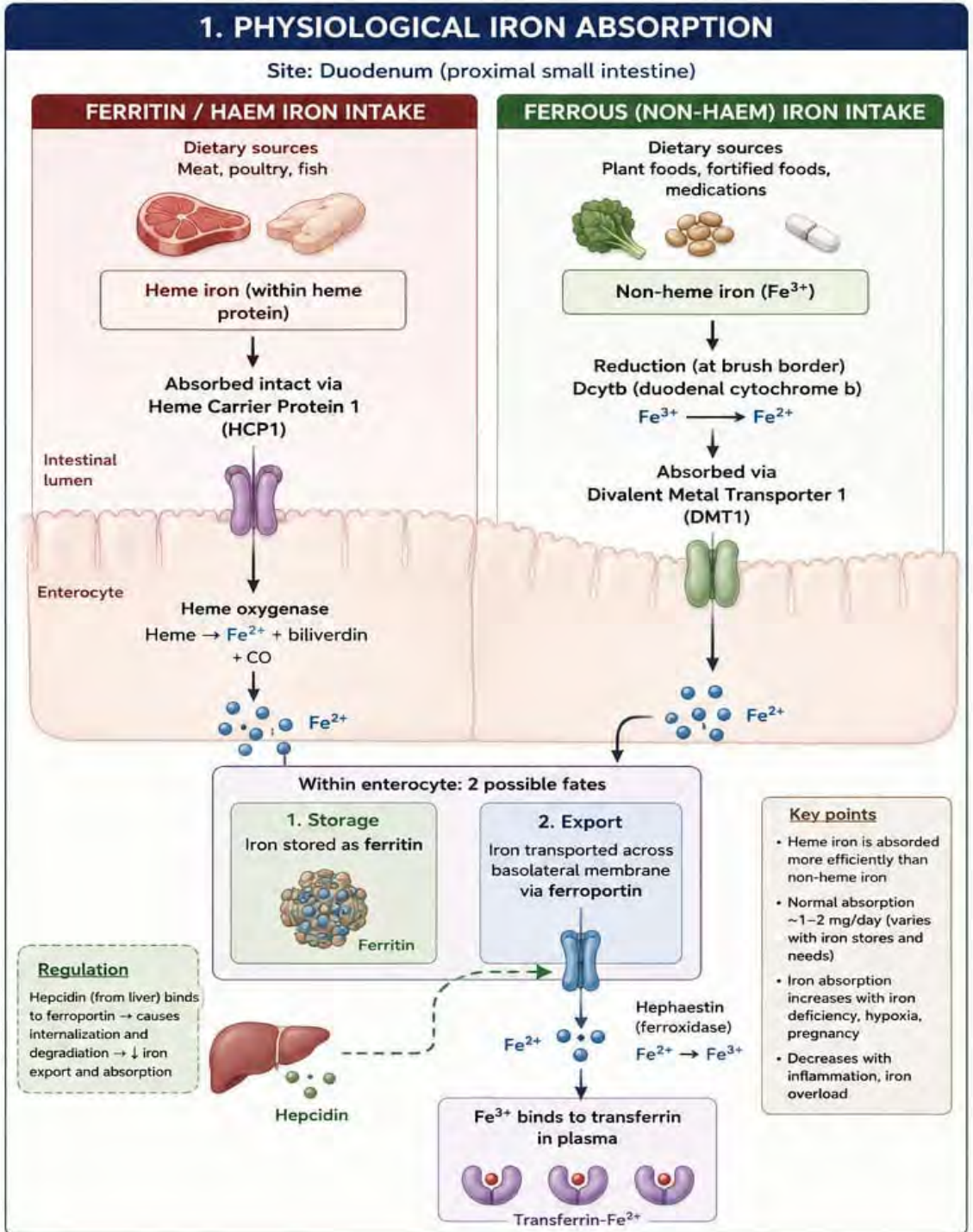
- After TG delivery, chylomicron remnants (rich in cholesterol, ApoE) are taken up by the liver via ApoE receptors.
- Cholesterol and lipids are reused or excreted in bile.

KEY PLAYERS

Bile Salts	Emulsify dietary fats and form micelles
Pancreatic Lipase	Hydrolyzes TG → FFA + Monoglycerides
ApoB-48	Structural protein for chylomicron assembly in enterocyte
HDL (ApoC-II, ApoE)	Donates ApoC-II (activates LPL) and ApoE (remnant uptake)
LPL	Hydrolyzes TG in chylomicrons → FFA for tissues
ApoE	Mediates remnant clearance by the liver

THE JOURNEY AT A GLANCE

1 Lumen → 2 Enterocyte → 3 Re-esterify & Assemble → 4 Lymph → 5 Blood (HDL Mediated) → 6 Tissues (FFA) → 7 Liver (Remnant)

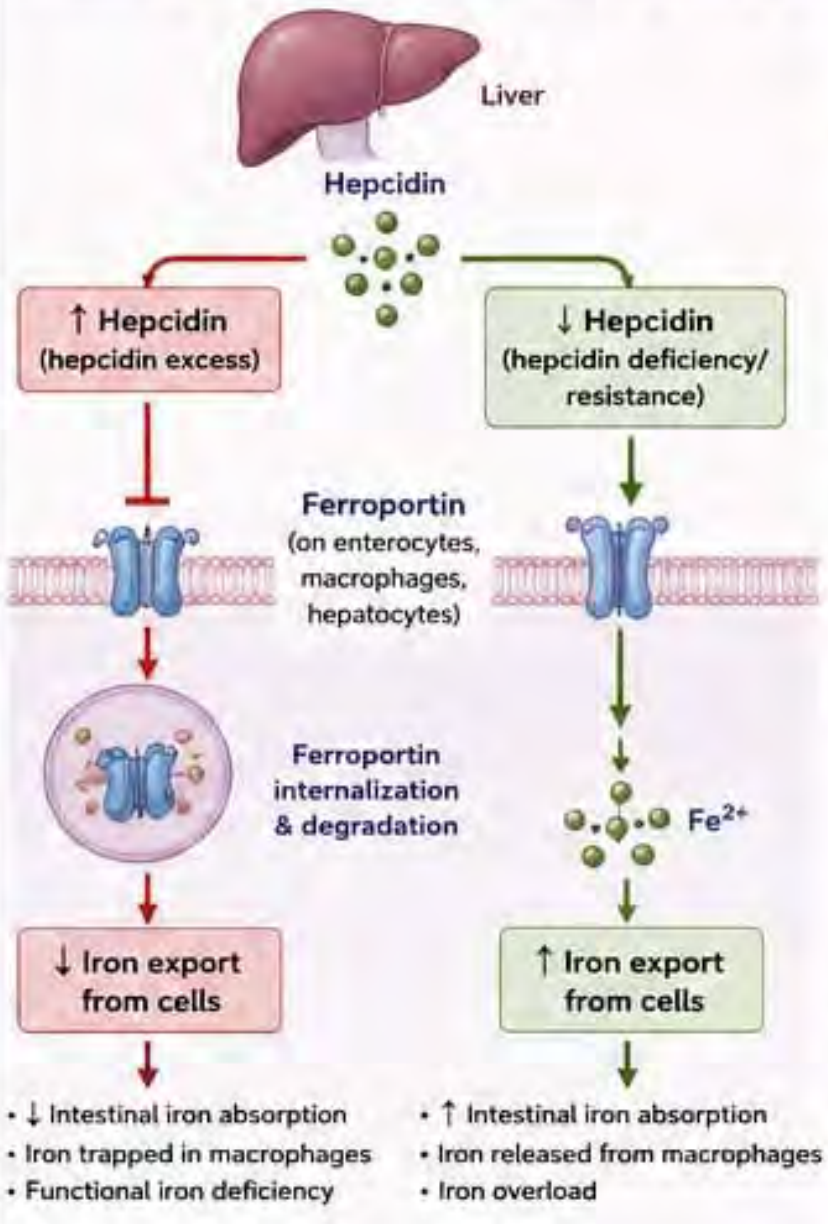


Iron absorption

- Haem iron better absorbed over non-haem iron
- Non-haem Fe3+ require dissolution in low pH (stomach) & reduction to Fe2+ by brush border ferrireductase/Dcytb
- Haem -> HCP1
- Non-haem -> DMT1 / NRAMP2
- Iron signalling to gut
  - Determines absorptive capacity of developing crypt cell
  - Store as ferritin in cell for shedding
- Ferroportin + hephaestin
  - Hepcidin

2. PATHOLOGICAL PROCESSES

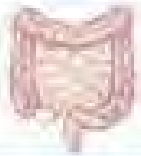
A. HEPCIDIN–FERROPORTIN AXIS IN DISEASE



CONDITION	HEPCIDIN	FERROPORTIN	EFFECT ON IRON
Anemia of chronic disease / inflammation	↑ Increased (IL-6 mediated)	↓ Decreased (degraded)	↓ Iron absorption, iron sequestration in macrophages → functional iron deficiency
Iron deficiency (anemia)	↓ Decreased	↑ Increased	↑ Iron absorption and mobilization
Hereditary hemochromatosis (Type 1 – HFE related)	↓ Inappropriately low	↑ Increased	↑↑ Iron absorption → iron overload
Type 2A (HJV – juvenile hemochromatosis)	↓ Very low/absent	↑ Increased	Severe iron overload, early onset
Type 2B (HAMP – hepcidin deficiency)	↓ Absent	↑ Increased	Severe iron overload
Type 3 (TFR2 related)	↓ Inappropriately low	↑ Increased	Iron overload
Type 4A (SLC40A1 – ferroportin disease)	Normal or ↑	Ferroportin resistant	Iron overload (milder/variable)

Key idea: Hepcidin is the master regulator. Too much hepcidin → iron deficiency of inflammation. Too little or no hepcidin activity → iron overload (hemochromatosis).

B. CAUSES OF POOR IRON ABSORPTION

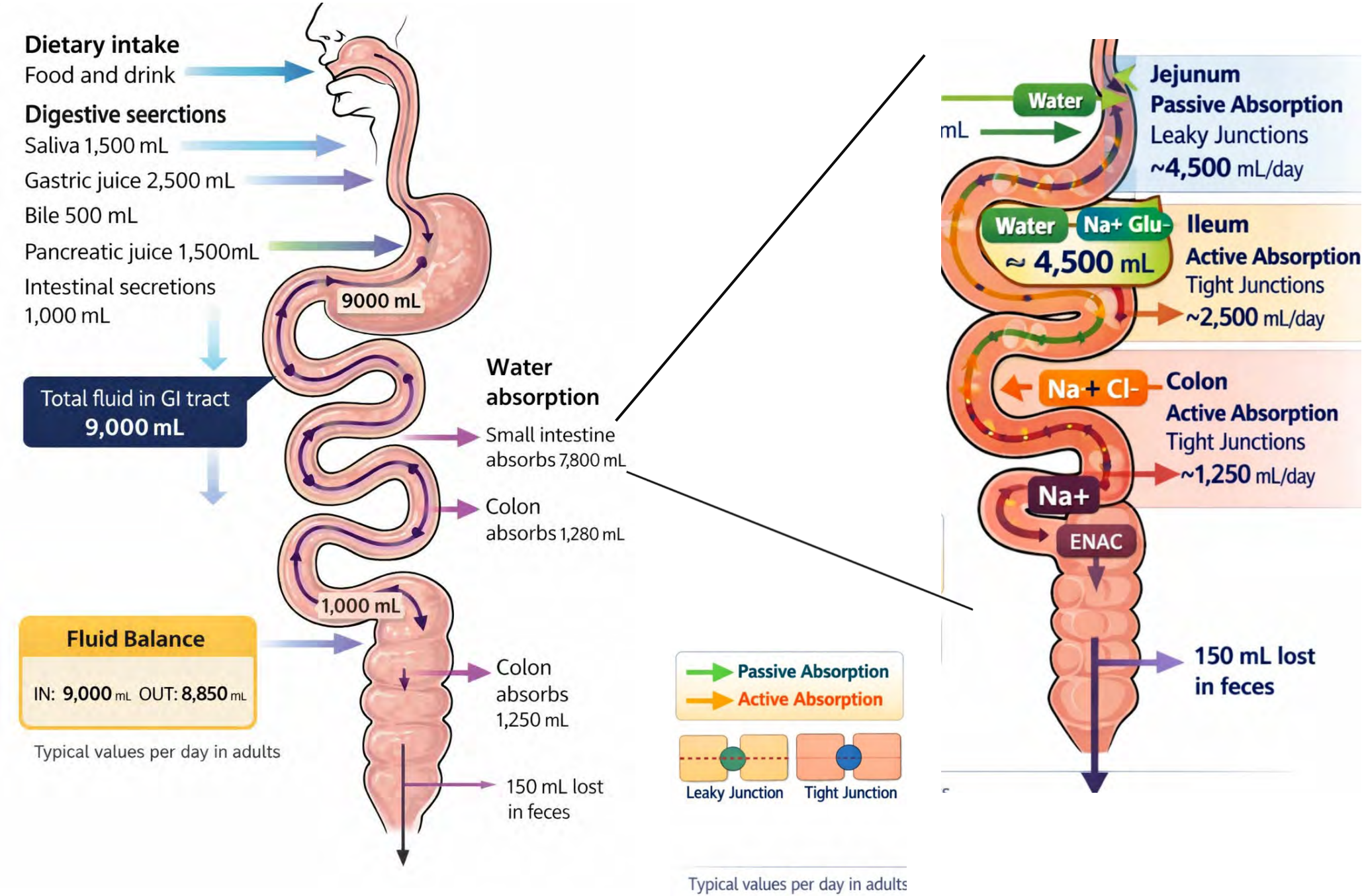
 **Reduced gastric acid** (achlorhydria, PPI therapy, atrophic gastritis)	Low acid impairs conversion of Fe^{3+} to Fe^{2+} and reduces iron solubility
 **Intestinal disorders** (celiac disease, IBD, atrophic gastritis)	Mucosal damage or inflammation reduces absorptive surface and transporter function
 **Post-surgical states** (gastrectomy, bariatric surgery, bypass)	Reduced surface area or bypass of duodenum/jejunum (site of iron absorption)
 **Medications** (PPIs, antacids, sucralfate, cholestyramine)	Increase gastric pH or bind iron → reduced absorption
 **Dietary factors** (low dietary iron, vegetarian/vegan diets)	Lower iron intake → less iron available for absorption
 **Inhibitory dietary substances** (phytates, calcium, tannins, polyphenols, soy)	Bind iron or inhibit transport → reduced absorption
 **Chronic inflammation / high hepcidin** (infections, CKD, autoimmune disease)	Hepcidin excess decreases ferroportin activity → reduces intestinal iron absorption

- Potassium (small bowel >> colon)
  - Mostly passive via paracellular (also Na/K ATPase, BK K channels)
  - Losses vulnerable in most diarrhoeal illnesses esp villous adenoma
- Calcium (duodenum)
  - Vit D dependent TRPV6 -> calbindin -> PMCA1b or Na/Ca exchanger
  - Some passive absorption (achlorhydia may impair Ca salt solubility)
- Magnesium (distal small bowel/colon)
  - Passive paracellular and active via TRPM6
  - ?PPI
- Phosphate
  - Passive paracellular and active via NaPi-IIb

- Vitamin K (jejunum/ileum)
  - K1 (plant sources)
  - K2 (gut bacteria)
- Folate (duodenum/prox jej)
  - Mostly from diet (fortified foods) & some from bacteria
  - Brush border: poly->monoglutamate folate
  - Apical transporter PCFT
- B12

Jejunum

- ~2.5m
- Difficult to discern between ileum
  - After duodenum proximal 2/5ths with ileum distal 3/5ths of SI
  - Thicker walls
  - Richer blood supply
  - Wider lumen (3cm)
- Occupies left upper & central abdomen
- High surface area
  - Tall plicae circulares / long villi / dense microvilli
- Responsible for majority of solute & water absorption


Dietary intake
Food and drink
Digestive seerctions
Saliva 1,500 mL
Gastric juice 2,500 mL
Bile 500 mL
Pancreatic juice 1,500mL
Intestinal secretions
1,000 mL
Total fluid in GI tract
9,000 mL
9000 mL
Water absorption
Small intestine absorbs 7,800 mL
Colon absorbs 1,280 mL
1,000 mL
Fluid Balance
IN: 9,000 mL OUT: 8,850 mL
Typical values per day in adults
Colon absorbs 1,250 mL
150 mL lost in feces
Passive Absorption
Active Absorption
Leaky Junction
Tight Junction
Typical values per day in adults
Water
mL
Jejunum
Passive Absorption
Leaky Junctions
~4,500 mL/day
Water
Na+ Glu-
≈ 4,500 mL
Ileum
Active Absorption
Tight Junctions
~2,500 mL/day
Na+ Cl-
Colon
Active Absorption
Tight Junctions
~1,250 mL/day
Na+
ENAC
150 mL lost in feces

Fluid absorption

- Passive absorption
  - Predominantly jejunum due to paracellular not-so-tight tight junctions
  - Driven by osmotic gradients with passive Na, glucose and water absorption
- Active absorption
  - Nutrient coupled Na – SGLT1 (jejunum)
  - Electroneutral NaCl absorption (jej + ileum)
    - NHE3
    - DRA: Cl/HCO3 exchanger NB CFTR in cholera / CF
  - Electrogenic Na absorption – ENaC
  - Minor aquapourin role

Ileum

- Longest segment of SI ~3.5m in central/lower Rt abdomen
- Peyer's patch
  - Covered by follicular associated epithelium (FAE)
  - M cells Ag phagocytosis/transcytosis
  - CCR5 important in Th1 immune response
    - Increased expression with excess Th1/Th17 in Crohn's
    - Important HIV-co receptor: largest HIV reservoir; HIV enteropathy
  - Activation leads to α4β7 expression
- B12 & bile salt absorption
- Ileal break & ileocaecal valve
  - L cells, GLP1/2, PYY

VITAMIN B12 ABSORPTION: FROM DIET TO SYSTEMIC CIRCULATION

1 DIET

Vitamin B12 is found in animal-based foods.

2 STOMACH (ANTRUM)

- Gastric acid and pepsin release B12 from food proteins.
- B12 binds to R-factor (haptocorrin) from saliva and gastric secretions.
- IF (intrinsic factor) is present but does not bind most B12 in the acidic stomach.

3 DUODENUM (KEY STEP)

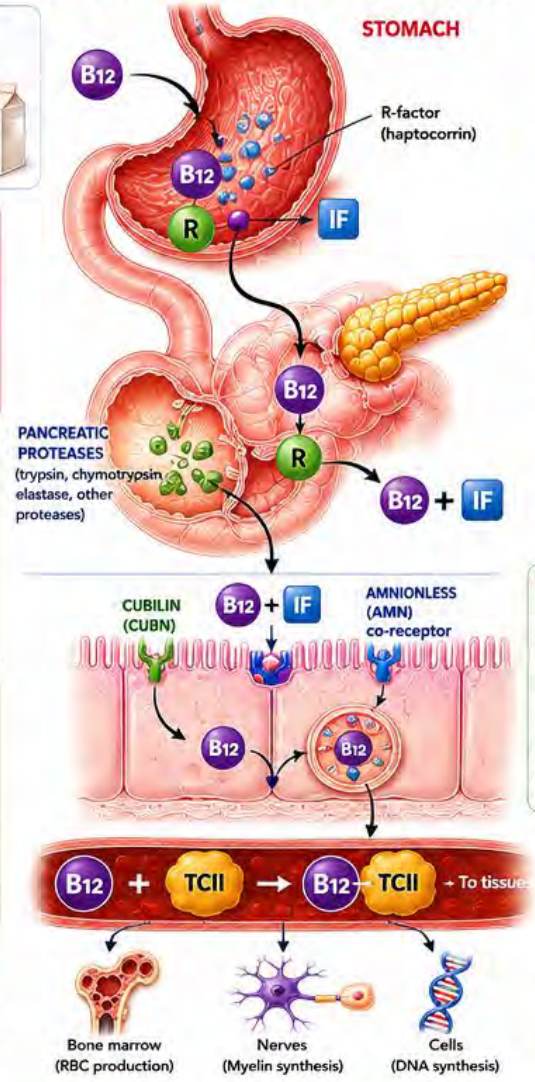
- Pancreatic proteases (trypsin, chymotrypsin, elastase, carboxypeptidases) **DEGRADE R-FACTOR** (haptocorrin).
- This releases B12.
- Free B12 then binds to Intrinsic Factor (IF).

4 TERMINAL ILEUM (ABSORPTION)

- The B12–IF complex binds to the cubilin (CUBN) receptor with amnionless (AMN) as co-receptor on enterocytes.
- Receptor-mediated endocytosis occurs.
- The complex is internalized and B12 is released inside the cell.

5 TRANSPORT IN BLOOD & CELLULAR UPTAKE

- Inside enterocyte, B12 binds to Transcobalamin II (TCII).
- B12–TCII complex enters blood.
- Cells take up B12–TCII via CD320 receptors.



KEY MOLECULES

- R = R-factor (haptocorrin)
- IF = Intrinsic Factor
- B12 = Vitamin B12
- TCII = Transcobalamin II
- CUBN = Cubilin receptor
- AMN = Amnionless

IMPORTANT:
R-factor is degraded by PANCREATIC proteases in the DUODENUM (not by stomach acid).

RARE INBORN ERRORS – CUBILIN PATHWAY

- Imerslund–Gräsbeck syndrome (CUBN gene mutation)
- Cubilin (CUBN) or Amnionless (AMN) gene defects

→ Absent/defective receptor complex → severe early-onset B12 malabsorption (megaloblastic anemia, failure to thrive)

B12 STORES & DURATION

- Total body stores: 2–5 mg (mainly in liver)
- Daily requirement: ~2–3 µg
- Stores last ~3–5 years even with poor intake.

SMALL PASSIVE ABSORPTION (~1%)

About ~1% of ingested B12 is absorbed passively along the entire intestine by diffusion, independent of intrinsic factor. This small amount can prevent deficiency in normal intake but is insufficient in deficiency states or after total gastrectomy.

HOW NITROUS OXIDE (N_2O) INTERFERES WITH B12

Nitrous oxide (N_2O) oxidizes cobalt from the cobalt reabalt (Co^+) in cobalamin from Co^+ to Co^{2+} (inactive).

Co^+ (active) methionine synthase

Co^{2+} (inactive)

RESULT: Inactive B12 → methionine synthase blocked → impaired DNA synthesis → megaloblastic anemia and neurologic dysfunction.

Risk groups:

- Recreational or occupational N_2O use
- Repeated anesthesia exposure
- Malnutrition
- Preexisting low B12

HOW METFORMIN CAUSES B12 DEFICIENCY

Metformin interferes with calcium-dependent membrane action in the terminal ileum → impaired absorption of the B12–IF complex.

Risk increases with:

- Higher dose (≥1500–2000 mg/day)
- Long duration (≥4 years)
- Older age
- Low B12 intake

Monitor B12 levels periodically in long-term metformin users.

HOW DISEASE PROCESSES CAN CAUSE LOW VITAMIN B12 LEVELS

SITE / STEP AFFECTED	EXAMPLES OF DISEASE PROCESSES	MECHANISM → EFFECT
DIETARY INTAKE	• Strict vegan diet • Malnutrition • Alcohol use disorder • Eating disorders	Inadequate intake → Low body stores over time
STOMACH – HCL PRODUCTION (Release of B12 from food)	• Chronic atrophic gastritis (autoimmune) • Pernicious anemia • *H. pylori* infection • Partial/total gastrectomy • Long-term PPI or H2 blocker use	↓ Stomach acid → impaired release of B12 from food proteins
STOMACH – R-FACTOR (HAPTOCORRIN) (Initial binding)	• Achlorhydria (autoimmune gastritis) • Pernicious anemia • *H. pylori* infection • Gastrointestinal surgery • Long-term PPI or H2 blocker use	↓ R-factor production or abnormal R-factor → less B12 bound initially
DUODENUM – PROTEOLYTIC DEGRADATION OF R-FACTOR (KEY STEP)	• Pancreatic insufficiency (chronic pancreatitis, cystic fibrosis, pancreatectomy) • Small intestinal bacterial overgrowth (SIBO) • Severe maldigestion syndromes	Pancreatic proteases fail to degrade R-factor → B12 remains bound to R-factor and cannot bind IF
INTRINSIC FACTOR PRODUCTION (Binding partner for B12)	• Pernicious anemia (autoimmune destruction of parietal cells) • Partial or total gastrectomy • Rare congenital IF deficiency	↓ Intrinsic Factor → B12 cannot bind IF
TERMINAL ILEUM – ABSORPTION (Ileal receptor-mediated uptake)	• Crohn disease (ileal involvement) • Celiac disease • Ileal resection or bypass • Radiation enteritis	Damaged/absent ileal mucosa or cubilin/amnionless receptors → B12–IF complex not absorbed
RARE INBORN ERRORS – CUBILIN PATHWAY	• Imerslund–Gräsbeck syndrome (CUBN gene mutation) • Cubilin (CUBN) or Amnionless (AMN) gene defects	Absent/defective cubilin or amnionless → severe early-onset B12 malabsorption
BACTERIAL OVERGROWTH OR FISH TAPEWORM	• Small intestinal bacterial overgrowth (SIBO) • *Diphyllobothrium latum* (fish tapeworm) • Other intestinal parasites	Bacteria/parasite consume B12 → reduced B12 available for absorption
TRANSPORT / UTILIZATION (AFTER ABSORPTION)	• Liver disease (↓ TCII production) • Congestive heart failure • Drugs: nitrous oxide, metformin, colchicine • Rare transcobalamin II deficiency	Impaired transport, release or cellular uptake/use → low functional B12

KEY TAKE-HOME POINTS

- R-factor (haptocorrin) binds B12 in the stomach.
- It is degraded by pancreatic proteases in the duodenum, releasing B12 to bind intrinsic factor.
- IF–B12 is absorbed in the terminal ileum via cubilin/amnionless.
- ~1% passive absorption occurs without IF along the gut.
- B12 stores are large and last ~3–5 years.
- Nitrous oxide inactivates B12 and causes functional deficiency.
- Metformin reduces B12 absorption—monitor with long-term use.

Bile salt absorption

Bile salts more than just a fat delivery system
- *important endocrine & antimicrobial molecule*

- Cholesterol -> CYP7A1 -> cholic/chenodeoxycholic acid
- Conjugated with glycine (75%) or taurine (25%)
- Hepatocytes -> BSEP -> canaliculi -> bile flow
- GB storage -> CCK -> duodenum
- Emulsify fat -> micelles with trigs presented to lipase
- Micelles deliver fats/ADEK -> bile salt remains in lumen
- 95% absorbed in TI via ASBT -> FXR -> FGF19 -> OATP/NTCP -> liver
- TGR5

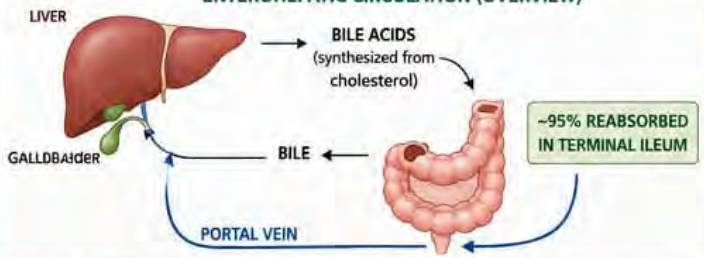
BAM: SeHCAT <15% day 7

A. BILE ACID SALT ABSORPTION FROM TERMINAL ILEUM – FGF19 SIGNALING & FXR INTERACTION

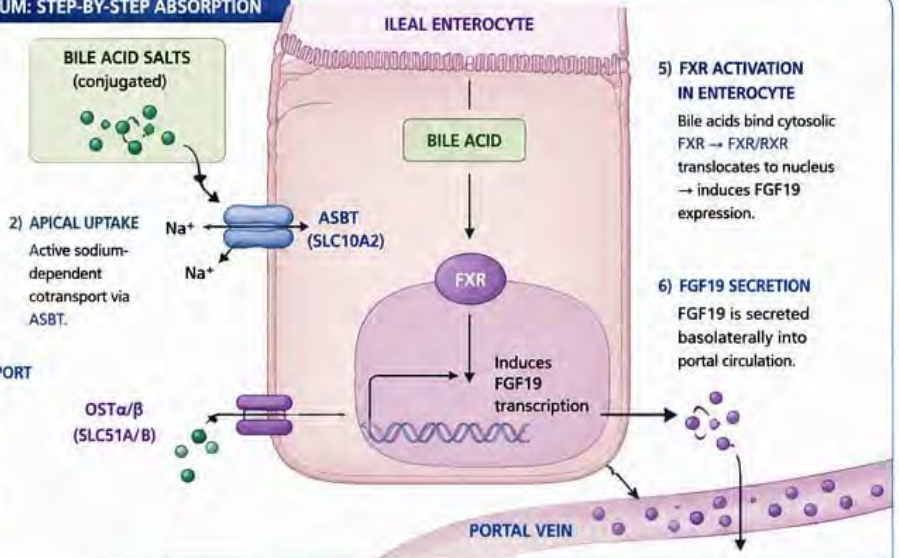
THE BIG PICTURE

- ~95% of bile acids are reabsorbed in the terminal ileum and recycled via the enterohepatic circulation.
- Key sensors: FXR in ileal enterocytes → induces FGF19 → signals the liver to ↓ bile acid synthesis and ↑ uptake.

ENTEROHEPATIC CIRCULATION (OVERVIEW)



TERMINAL ILEUM: STEP-BY-STEP ABSORPTION



1) LUMEN
Bile acids are predominantly in their ionized form (pKa ~6) and exist as bile acid salts (conjugated to glycine or taurine).

2) APICAL UPTAKE
Active sodium-dependent cotransport via ASBT.

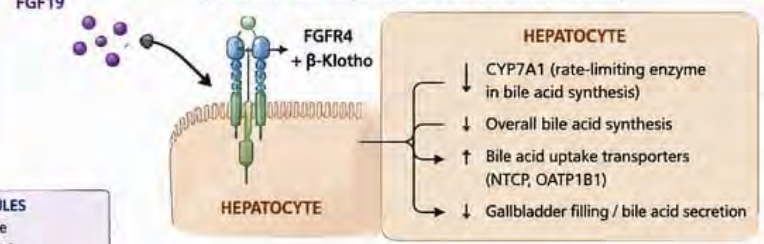
3) BASOLATERAL EXPORT
Bile acids exit the cell via OSTα/β (heterodimer).

4) TO PORTAL VEIN
Bile acids travel via portal blood back to the liver.

5) FXR ACTIVATION IN ENTEROCYTE
Bile acids bind cytosolic FXR → FXR/RXR translocates to nucleus → induces FGF19 expression.

6) FGF19 SECRETION
FGF19 is secreted basolaterally into portal circulation.

7) HEPATIC ACTIONS OF FGF19 (via FGFR4/β-Klotho)



CLINICAL PEARL

- ASBT is the rate-limiting step of bile acid reabsorption.
- ~5% of bile acids escape reabsorption and are lost in stool (major route of cholesterol excretion).

KEY TRANSPORTERS & MOLECULES

ASBT (SLC10A2) – Apical bile acid uptake
OSTα/β (SLCS1A/ B) – Basolateral export
FXR – Nuclear receptor for bile acids
FGF19 – Ileal hormone
FGFR4/β-Klotho – Hepatic receptor complex
CYP7A1 – Cholesterol 7α-hydroxylase

- Ileal resection (>100 cm) →
  - bile acid malabsorption & chronic diarrhea.
- FXR agonists increase FGF19
  - and suppress bile acid synthesis size in check.

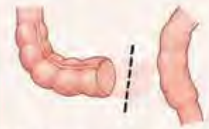
CLINICAL PEARLS (PEARLS OF WISDOM)

- Ileal resection (>100 cm) → bile acid malabsorption.
- Bile acids are signaling molecules, not just detergents.
- FGF19 is a negative feedback hormone to keep bile acid pool size in check.
- FXR agonists increase FGF19 and suppress bile acid synthesis.

B. WHEN IT GOES WRONG: PATHOLOGY & THERAPEUTIC TARGETS

PATHOLOGY: WHERE THE SYSTEM FAILS

1 ILEAL DISEASE OR RESECTION
(↓ ASBT-mediated reabsorption)



- Crohn disease (terminal ileitis)
- Ileal resection (>100 cm)
- Radiation enteritis

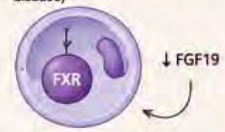
↓

BILE ACID MALABSORPTION

Excess bile acids in colon → secretory diarrhea, urgency, bloating, fecal incontinence

2 FXR / FGF19 SIGNALING DEFECTS

- Reduced FXR activity (genetic variants, inflammation, drugs)
- ↓ FGF19 production (ileal disease)



Loss of negative feedback

↑ CYP7A1 activity
↑ Bile acid synthesis
Enlarged bile acid pool
→ Cholestatic liver injury or steatosis over time

3 CHANGES IN BILE ACID POOL

- Dysbiosis alters bile acid composition (↓ secondary BAs)
- More hydrophobic bile acids

Can cause:

- Hepatocyte injury
- Inflammation
- Fibrosis progression

4 INCREASED INTESTINAL LOSS
(↑ CYP7A1, ↓ reabsorption)

More bile acids lost in stool → increased cholesterol catabolism → dyslipidemia

THERAPEUTIC TARGETS: RESTORING BALANCE

TARGET / STRATEGY	MECHANISM	EXAMPLES	CLINICAL USE / NOTES
BILE ACID SEQUESTRANTS (BAS)	Bind bile acids in intestine → prevent colonic irritation → increase fecal excretion	Cholestyramine Colesevelam Colestipol	First-line for bile acid diarrhea (Pruritus in cholestasis) ↓ LDL-C
ASBT INHIBITORS	Block ileal bile acid uptake → increase fecal excretion	Elobixibat (Odevixibat)	Ileal bile acid malabsorption disorders (under evaluation)
FXR AGONISTS	Activate FXR → ↑ FGF19 → ↓ bile acid synthesis, anti-inflammatory, ↓ fibrosis	Obeticholic acid (semisynthetic) EDP-305 (investigational)	Primary biliary cholangitis (OCA) Nonalcoholic steatohepatitis (under study)
FGF19 ANALOGS	Mimic FGF19 → ↓ CYP7A1, ↓ bile acid synthesis	Aldafermin (NGM282) Pegbelfermin (BMS-986036)	NASH, PBC, cholestatic pruritus (clinical trials)
MICROBIOME MODULATION	Restore secondary bile acid formation & pool balance	Probiotics Fecal microbiota therapy Dietary fiber	Investigational; may improve metabolic & liver diseases
UDCA (URSODEOXYCHOLIC ACID)	Hydrophilic BA → replaces hydrophobic BAs, choleretic, cytoprotective	Ursodiol	PBC, PSC, some cholestatic conditions

KEY CLINICAL PEARLS

- Bile acids are hormones: think "FXR → FGF19 → feedback."
- Bile acid diarrhea responds dramatically to sequestrants.
- In cholestatic diseases, modulating FXR/FGF19 improves bile flow and reduces injury.
- Future therapies: dual ASBT + FXR modulation for metabolic and cholestatic diseases.

REMEMBER

The ileum isn't just a passive pipe—it's the control center that senses bile acids and tells the liver how much more to make.

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