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CHAPTER 4

SMALL BOWEL DISEASES, DIARRHEA & MALABSORPTION

CELIAC DISEASE | CROHN'S DISEASE (SMALL BOWEL) | INFECTIOUS DIARRHEA | MALABSORPTION SYNDROMES

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Dedication

In loving memory of my mother,

who recently returned to the mercy of Allah.

Her love, prayers, patience, and sacrifices were among the greatest blessings of my life. Whatever good I achieve carries something of her guidance and support.

May Allah forgive her, have mercy upon her, illuminate her grave, and grant her the highest place in **Jannat al-Firdaws**.

This work is dedicated to her memory.

أسأل الله أن يرحم أمي رحمة واسعه وأن يدخلها الفردوس الأعلى من الجنة، ورجاءً أسألكم لها خالص الدعاء..

Chapter 4: Small Bowel Diseases, Diarrhea & Malabsorption

50 Difficult Consultant-Level Mechanism-Based MCQs

Design: **advanced fellowship style**, **mechanism-based reasoning**, **randomized correct-answer positions**, and **colored bold high-yield keywords**.

Uploaded source basis: ACG guideline collection, Sleisenger & Fordtran, Gastrointestinal and Liver Secrets, CURRENT Diagnosis & Treatment, and Gastroenterology Clinical Focus. Questions are original and not copied from source questions.

Answer Key

1. D	2. C	3. B	4. D	5. A	6. C	7. B	8. E	9. C	10. A
11. E	12. B	13. D	14. C	15. B	16. B	17. E	18. C	19. C	20. B
21. A	22. A	23. C	24. B	25. A	26. B	27. C	28. E	29. B	30. D
31. A	32. B	33. C	34. C	35. D	36. A	37. C	38. B	39. A	40. D
41. E	42. C	43. B	44. C	45. C	46. D	47. B	48. A	49. A	50. D

1. Celiac disease on gluten-free diet: HLA exclusion logic

A 32-year-old woman started a **gluten-free diet** 9 months before referral because of bloating and fatigue. She now has negative **tTG-IgA**, normal duodenal biopsies, and no documented pre-diet histology. She wants to know whether a prolonged gluten challenge is necessary. **HLA-DQ2/DQ8** testing is negative.

Which interpretation is most mechanism-based?

A. Negative serology after a gluten-free diet confirms celiac disease remission and proves prior celiac disease.

B. Normal biopsies while gluten-free exclude celiac disease with the same certainty as HLA testing.

C. A gluten challenge is mandatory because HLA testing has poor negative predictive value.

D. Absence of both HLA-DQ2 and HLA-DQ8 makes celiac disease extremely unlikely and usually avoids gluten challenge.

E. HLA-DQ2/DQ8 positivity is required to monitor adherence to a gluten-free diet.

Answer: D

Mechanism pearl: Celiac disease requires permissive **HLA-DQ2 or HLA-DQ8** antigen presentation in almost all cases. A negative result is useful because of its **high negative predictive value**, especially when serology and biopsy were performed after gluten withdrawal.

2. Celiac immunopathogenesis: tTG and HLA binding

A 24-year-old man with iron deficiency anemia and chronic diarrhea has positive **tTG-IgA** and villous atrophy. His biopsy shows increased intraepithelial lymphocytes and crypt hyperplasia. A fellow says gluten is toxic simply because it is osmotically active.

Which molecular event best explains the immune disease process?

A. Gliadin directly opens CFTR channels, producing secretory diarrhea independent of immunity.

B. Brush-border lactase converts gluten into a poorly absorbed osmole, producing villous atrophy.

C. Tissue transglutaminase deamidates gliadin, creating negatively charged peptides that bind HLA-DQ2/DQ8 and activate mucosal T cells.

D. Secretory IgA binds gliadin and blocks antigen presentation, causing compensatory crypt hyperplasia.

E. Pancreatic proteases cross-link gliadin to bile acids, producing toxic micelles.

Answer: C

Mechanism pearl: The key mechanism is **tTG-mediated deamidation** of gliadin, which improves binding to **HLA-DQ2/DQ8** and drives adaptive mucosal T-cell activation with villous injury.

3. IgA deficiency and false-negative celiac serology

A 41-year-old woman has weight loss, osteopenia, and diarrhea. Duodenal biopsy shows subtotal villous atrophy. **tTG-IgA** is negative, but total serum **IgA** is markedly low.

Which next test is most biologically appropriate?

A. Antigliadin IgA because IgA deficiency increases its sensitivity.

B. IgG-based celiac serology, such as IgG deamidated gliadin peptide or IgG tTG.

C. Serum VIP because villous atrophy is usually endocrine.

D. Fecal elastase because pancreatic insufficiency causes subtotal villous atrophy.

E. Stop evaluation because negative tTG-IgA excludes celiac disease.

Answer: B

Mechanism pearl: In **IgA deficiency**, IgA-based serology may be falsely negative. Mechanism-based testing shifts to **IgG-based celiac assays** and histologic correlation.

4. Patchy celiac disease and biopsy strategy

A 29-year-old woman with type 1 diabetes and iron deficiency has a normal-looking duodenum at endoscopy. The endoscopist plans to avoid biopsy because there is no scalloping or fold loss.

Which explanation best justifies biopsy despite normal endoscopic appearance?

A. Endoscopic scalloping has perfect sensitivity, but biopsy is required for Marsh staging only.
B. Celiac disease affects only the ileum, so terminal ileal biopsy should replace duodenal sampling.
C. Normal endoscopy excludes celiac disease if tTG-IgA is positive.
D. Multiple distal duodenal and bulb biopsies increase yield because mucosal injury can be patchy and endoscopic signs have limited sensitivity.
E. Biopsy is unnecessary if the patient has any autoimmune disease.

Answer: D

Mechanism pearl: Celiac injury can be **patchy**, and endoscopic markers such as **scalloping** have limited sensitivity. Multiple biopsies, including **duodenal bulb** sampling when clinically suspected, improve detection.

5. Lymphocytic duodenosis: not synonymous with celiac disease

A 55-year-old man has dyspepsia and duodenal biopsies showing increased intraepithelial lymphocytes but normal villous architecture. tTG-IgA is negative and he uses NSAIDs intermittently. His trainee labels this as definite celiac disease.

Which interpretation is most accurate?

A. Lymphocytic duodenosis without villous atrophy is nonspecific and requires clinical, serologic, medication, infectious, and histologic correlation.
B. Increased intraepithelial lymphocytes alone confirm refractory celiac disease type II.
C. Normal villi exclude all gluten-related disorders and all small bowel disease.
D. NSAID exposure makes celiac serology falsely positive, so biopsy alone is definitive.
E. The finding is diagnostic of pancreatic exocrine insufficiency.

Answer: A

Mechanism pearl: **Lymphocytic duodenosis** is a pattern, not a diagnosis. Without **villous atrophy** or supportive serology, consider celiac disease plus mimics such as medications, infections, immune disorders, and Crohn-related disease.

6. Dermatitis herpetiformis as cutaneous celiac disease

A 36-year-old man has grouped intensely pruritic vesicles over elbows and knees, mild diarrhea, and iron deficiency. Small-bowel symptoms are subtle. Skin biopsy with immunofluorescence is planned.

Which immunologic finding best explains the diagnosis?

A. Linear IgG along the basement membrane from anti-collagen VII antibodies.
B. Dense dermal eosinophils driven by IL-5 without gluten sensitivity.
C. Granular IgA deposition related to transglutaminase autoimmunity at the dermoepidermal junction.
D. Monoclonal IgM rheumatoid factor immune complexes in dermal vessels.
E. Perivascular IgG4 plasma cells with storiform fibrosis.

Answer: C

Mechanism pearl: **Dermatitis herpetiformis** is strongly linked to celiac disease and shows **granular IgA deposition** in skin, reflecting transglutaminase-related autoimmunity.

7. Nonresponsive celiac disease: first mechanistic step

A 47-year-old woman with biopsy-proven celiac disease remains symptomatic after 8 months of a declared strict gluten-free diet. Repeat tTG remains positive. She has no alarm features.

Which explanation should be prioritized first?

A. Type II refractory celiac disease is proven by persistent positive serology.
B. Persistent positive serology suggests ongoing gluten exposure and requires expert dietary review before labeling refractory disease.
C. Small bowel lymphoma is the most common cause of persistent tTG positivity.
D. Pancreatic insufficiency causes persistent tTG positivity through antigen cross-reactivity.
E. Positive tTG after treatment indicates irreversible villous atrophy.

Answer: B

Mechanism pearl: In **nonresponsive celiac disease**, persistent positive serology after dietary treatment usually points to **ongoing gluten ingestion** before true **refractory celiac disease** is considered.

8. Refractory celiac disease type II and lymphoma biology

A 61-year-old man with proven celiac disease has persistent malabsorption and villous atrophy despite more than 12 months of supervised gluten avoidance. Flow cytometry shows an expanded aberrant intraepithelial lymphocyte population that is surface CD3-negative but cytoplasmic CD3-positive, lacks CD8, and has clonal T-cell receptor rearrangement.

Which complication is most mechanistically linked to this finding?

A. Gastrinoma from MEN1-mediated parietal cell stimulation.
B. Duodenal adenoma from APC pathway activation.
C. Microscopic colitis due to subepithelial collagen deposition.
D. Intestinal methanogen overgrowth due to Methanobrevibacter smithii.
E. Enteropathy-associated T-cell lymphoma arising from clonal aberrant intraepithelial lymphocytes.

Answer: E

Mechanism pearl: Type II refractory celiac disease is defined by **aberrant/clonal IELs** and is a premalignant lymphoproliferative state with risk of **enteropathy-associated T-cell lymphoma**.

9. Celiac crisis: severe malabsorptive physiology

A 70-year-old man with no prior diagnosis presents with profuse diarrhea, edema, hypokalemia, hypoalbuminemia, and metabolic derangements. Biopsies later show severe celiac enteropathy. Stool cultures are negative.

Which mechanism best explains the acute syndrome?

A. VIP-secreting pancreatic tumor causing isolated chloride secretion without mucosal injury.
B. Primary pancreatic enzyme deficiency with preserved mucosal absorption.
C. Severe immune-mediated small bowel mucosal injury causing life-threatening malabsorption and fluid-electrolyte loss.
D. Colon-limited collagen band deposition with no small-bowel involvement.
E. Loss of ileocecal valve causing only methane-predominant constipation.

Answer: C

Mechanism pearl: Celiac crisis is a rare severe presentation with major **malabsorption**, fluid loss, electrolyte disturbance, and hypoalbuminemia from intense small-bowel enteropathy.

10. Celiac-associated transaminitis

A 28-year-old woman has mild persistent aminotransferase elevation, iron deficiency, low vitamin D, bloating, and no viral, autoimmune, or metabolic liver diagnosis. She has no jaundice. A colleague suggests liver biopsy first.

Which mechanism-based action is more appropriate?

A. Screen for celiac disease because mild nonspecific hepatitis can accompany untreated celiac enteropathy.
B. Diagnose autoimmune hepatitis because celiac disease never affects liver tests.
C. Treat as Wilson disease because iron deficiency is diagnostic.
D. Order ERCP because celiac disease causes obstructive cholangitis.
E. Ignore the abnormal liver tests because malabsorption cannot affect hepatology.

Answer: A

Mechanism pearl: Untreated **celiac disease** can present with mild, otherwise unexplained **transaminitis**; screening is rational when malabsorptive clues coexist.

11. SIBO in scleroderma: motility and micronutrient signature

A 58-year-old woman with systemic sclerosis develops bloating, flatulence, weight loss, macrocytosis, low vitamin B12, high folate, and steatorrhea.

Which mechanism best integrates these findings?

A. Secretin receptor activation causing acid hypersecretion and lipase inactivation.
B. Autoimmune villous atrophy from tTG-mediated gliadin presentation.
C. Increased ileal bile acid uptake causing constipation and folate deficiency.
D. Pancreatic acinar destruction causing low folate and high B12.
E. Small-bowel stasis permits bacterial overgrowth, bile salt deconjugation, B12 consumption, and bacterial folate production.

Answer: E

Mechanism pearl: Scleroderma dysmotility disrupts clearance and the **migrating motor complex**, promoting **SIBO**. Bacteria deconjugate **bile salts**, consume **B12**, and may produce **folate**.

12. Breath testing: hydrogen and methane biology

A patient with bloating undergoes lactulose breath testing. Hydrogen rises early, then rises again later. Methane is persistently >10 ppm. The report labels this as simple bacterial overgrowth only.

Which interpretation is most precise?

A. Humans generate hydrogen during carbohydrate absorption, so an early rise is physiologic.
B. Hydrogen reflects microbial fermentation; methane reflects methanogenic archaea using hydrogen substrate, so methane-predominant results may represent intestinal methanogen overgrowth.
C. Methane proves colitis because bacteria in the colon cannot produce hydrogen.
D. Breath tests are definitive and have no false positives or false negatives.
E. A second hydrogen peak excludes small intestinal fermentation.

Answer: B

Mechanism pearl: Human cells do not produce breath **hydrogen** or **methane**. Hydrogen indicates microbial fermentation; **methane** production is mainly by methanogenic archaea such as **Methanobrevibacter smithii**.

13. SIBO aspirate culture: diagnostic strength and trap

A man with a blind loop after Billroth II surgery has suspected SIBO. Duodenal aspirate culture grows 10^4 CFU/mL. Another sample from the same patient is negative.

Which statement best explains the discrepancy?

A. Any negative aspirate excludes SIBO because bacterial overgrowth is uniformly distributed.

B. Culture is useless because more than 10^9 CFU/mL is required for diagnosis.

C. Aspirate culture measures methane only, not bacterial density.

D. Duodenal aspirate culture can support diagnosis, but sampling contamination and patchy overgrowth can produce discordant results.

E. Culture is positive only in celiac disease, not in blind-loop syndromes.

Answer: D

Mechanism pearl: Aspirate culture is a direct test for **SIBO** and counts can be diagnostic, but **patchiness** and **oropharyngeal contamination** limit interpretation.

14. Blind-loop steatorrhea and bile acid deconjugation

A 63-year-old man with a jejunal diverticular segment has bloating, low B12, high folate, and bulky stools. Pancreatic imaging is normal.

Which luminal mechanism best explains the steatorrhea?

A. Bacteria increase bile acid conjugation, causing excessive micelle formation.

B. Bacteria destroy enterocyte apolipoprotein B, preventing chylomicron assembly.

C. Bacterial deconjugation makes bile salts less effective detergents and reduces their intraluminal availability for micelle formation.

D. Methane-producing archaea directly inhibit pancreatic lipase secretion.

E. Gluten deamidation prevents bile acid reabsorption.

Answer: C

Mechanism pearl: In **SIBO**, bacteria **deconjugate bile salts**. Deconjugated bile salts are less soluble/effective as detergents and may be absorbed proximally, causing fat maldigestion.

15. SIBO host defense: why hypochlorhydria matters

A patient with autoimmune gastritis and pernicious anemia develops bloating and diarrhea. Breath testing suggests SIBO.

Which lost host defense best explains susceptibility?

A. Excess gastric acid delivery to the ileum.

B. Loss of gastric acid barrier permitting increased proximal small-bowel bacterial survival.

C. Increased secretory IgA killing of commensals.

D. Overactive ileocecal valve clearance.

E. Excess migrating motor complex activity during fasting.

Answer: B

Mechanism pearl: Normal **gastric acid** limits bacterial entry and survival in the proximal small bowel. **Hypochlorhydria/achlorhydria** is a recognized host-defense defect for SIBO.

16. Limited ileal resection: cholerheic diarrhea

A Crohn patient had 40 cm of terminal ileum resected. He develops watery diarrhea without steatorrhea. Symptoms improve with cholestyramine.

Which mechanism best explains this response?

A. Bile acid pool depletion causes failure of micelle formation, and cholestyramine restores bile acids.

B. Unabsorbed bile acids reach the colon and stimulate secretion; sequestration binds them intraluminally.

C. Loss of jejunal lactase creates a high stool chloride state.

D. Pancreatic lipase is inactivated by gastric hypersecretion after ileal resection.

E. Ileal resection increases peptide YY and slows transit excessively.

Answer: B

Mechanism pearl: After limited **terminal ileal resection**, the liver can maintain the bile acid pool, but excess **bile acids spill into the colon**, causing secretory **cholerheic diarrhea** that responds to sequestrants.

17. Extensive ileal resection: why cholestyramine can worsen

A patient undergoes 160 cm terminal ileal resection. He develops steatorrhea, weight loss, and fat-soluble vitamin deficiency. Cholestyramine worsens his stools.

Which mechanism best explains this paradox?

A. Cholestyramine increases pancreatic lipase secretion and worsens fat digestion.
B. Extensive ileal resection increases bile acid synthesis enough to cause bile acid overload.
C. Ileal resection converts bile acids into chylomicrons that cannot enter lymphatics.
D. Cholestyramine directly damages enterocyte brush-border enzymes.
E. Severe bile acid loss depletes the bile acid pool, and sequestration further impairs micelle formation.

Answer: E

Mechanism pearl: With extensive ileal loss, the liver cannot compensate for fecal **bile acid loss**. The bile acid pool becomes depleted, causing **steatorrhea**; **cholestyramine** removes more bile acids and worsens fat malabsorption.

18. Ileal brake physiology

A patient with ileal resection has rapid transit and postprandial diarrhea disproportionate to measured fat malabsorption. His nutritionist asks about the ileal brake.

Which mechanism is most relevant?

A. The ileum secretes gastrin after fat exposure to accelerate gastric emptying.
B. Loss of ileal bile acid transport increases gastric acid neutralization.
C. Loss of ileal peptide YY feedback reduces slowing of upper GI motility after nutrient exposure.
D. The colon secretes secretin to suppress small bowel transit after resection.
E. The ileal brake is mediated only by pancreatic elastase.

Answer: C

Mechanism pearl: The **ileal brake** is nutrient-triggered feedback, partly through **peptide YY**, that slows proximal GI motility. Ileal loss removes this braking mechanism and worsens diarrhea.

19. Short bowel syndrome: citrulline as enterocyte-mass biomarker

Two patients have similar residual small-bowel length after resection. One remains dependent on parenteral nutrition. Plasma citrulline is markedly low.

Which interpretation best explains the biomarker?

A. Citrulline is produced mainly by pancreatic acinar cells and reflects enzyme secretion.
B. Citrulline rises when ileocecal valve loss is severe.
C. Low citrulline is a surrogate for reduced functional enterocyte mass and predicts intestinal failure risk.
D. Citrulline is a marker of bacterial methane production.
E. Citrulline directly measures bile acid concentration in stool.

Answer: C

Mechanism pearl: Citrulline is produced by enterocytes and can act as a biomarker of residual **enterocyte mass**. Low levels support more severe short-bowel intestinal failure biology.

20. Short bowel D-lactic acidosis

A woman with short bowel syndrome and intact colon develops episodic confusion, ataxia, dysarthria, and nystagmus after high-carbohydrate meals. Standard lactate is normal, but specialized testing shows D-lactate >3 mmol/L.

Which mechanism best explains the neurologic episodes?

A. Colonocytes fail to absorb water, causing acute hyponatremic encephalopathy.
B. Unabsorbed carbohydrate reaches the colon, where bacteria metabolize it to D-lactate that accumulates systemically.
C. Terminal ileal loss increases peptide YY, producing CNS sedation.
D. Bile acids activate NMDA receptors directly.
E. Pancreatic lipase deficiency produces ammonia through the urea cycle.

Answer: B

Mechanism pearl: In **short bowel syndrome** with colon continuity, unabsorbed carbohydrate can be fermented by colonic bacteria to **D-lactate**, producing episodic neurologic symptoms.

21. Enteric hyperoxaluria in short bowel

A patient with ileal resection, steatorrhea, and intact colon develops recurrent calcium oxalate renal stones. Urine oxalate is high.

Which mechanism best explains the stone risk?

A. Fat malabsorption causes calcium to bind unabsorbed fatty acids, leaving oxalate soluble and absorbable in the colon.
B. Loss of colon prevents oxalate absorption, increasing urinary oxalate.
C. Bile acid sequestrants convert oxalate into calcium carbonate.
D. D-lactate crystallizes with calcium in the kidney.
E. Medium-chain triglycerides directly increase oxalate synthesis.

Answer: A

Mechanism pearl: In **steatorrhea**, unabsorbed long-chain fatty acids bind luminal **calcium**. Less calcium is available to bind **oxalate**, so free oxalate is absorbed by an intact colon and excreted in urine.

22. Medium-chain triglycerides in lymphatic/postmucosal disease

A child with primary intestinal lymphangiectasia has edema, lymphopenia, hypoalbuminemia, and mild steatorrhea. A diet enriched with medium-chain triglycerides is recommended.

Which mechanism best explains this diet?

A. Medium-chain triglycerides are absorbed into portal blood and reduce dependence on chylomicron lymphatic transport.
B. Medium-chain triglycerides require more bile acids than long-chain fats and stimulate lymph flow.
C. Medium-chain triglycerides correct tTG-mediated gliadin presentation.
D. Medium-chain triglycerides are fermented to D-lactate and improve cognition.
E. Medium-chain triglycerides bind stool magnesium and lower osmotic gap.

Answer: A

Mechanism pearl: **Medium-chain triglycerides** bypass chylomicron-dependent lymphatic transport and enter the **portal circulation**, which helps when lymphatic transport is impaired.

23. Intestinal lymphangiectasia and protein-losing enteropathy

A young adult has chronic diarrhea, peripheral edema, chylous ascites, lymphopenia, low albumin, low immunoglobulins, and increased fecal alpha-1-antitrypsin clearance. Endoscopy shows whitish villi.

Which mechanism best explains the constellation?

A. Luminal bile acid deficiency from hepatic cholestasis alone.
B. Pancreatic bicarbonate deficiency causing acid-mediated villous blunting.
C. Leakage of protein- and lymphocyte-rich lymph into the intestinal lumen from ectatic or obstructed intestinal lymphatics.
D. HLA-DQ2-mediated gliadin presentation causing isolated IgA excess.
E. VIP-mediated cAMP activation causing hypochlorhydria without protein loss.

Answer: C

Mechanism pearl: **Intestinal lymphangiectasia** causes postmucosal transport failure: dilated lymphatics leak **albumin, immunoglobulins, and lymphocytes** into the gut, producing protein-losing enteropathy.

24. Malabsorption classification: intraluminal vs mucosal vs postmucosal

A trainee groups pancreatic insufficiency, celiac disease, and intestinal lymphangiectasia together as identical causes of malabsorption. The consultant asks for the dominant mechanism of each.

Which pairing is most accurate?

A. Pancreatic insufficiency - postmucosal transport failure; celiac - intraluminal maldigestion; lymphangiectasia - brush-border lactase loss.
B. Pancreatic insufficiency - impaired intraluminal digestion; celiac - impaired mucosal digestion/absorption; lymphangiectasia - impaired postmucosal lymphatic transport.
C. Pancreatic insufficiency - mucosal immune enteropathy; celiac - lymphatic leakage; lymphangiectasia - acid hypersecretion.
D. All three primarily cause osmotic diarrhea through magnesium retention.
E. All three are best distinguished by stool calprotectin alone.

Answer: B

Mechanism pearl: Difficult malabsorption questions often hinge on the dominant defect: **intraluminal digestion**, **mucosal absorption**, or **postmucosal transport**.

25. D-xylose test as mucosal absorption probe

A patient has steatorrhea. D-xylose absorption is normal, fecal elastase is low, and pancreatic calcifications are seen on CT.

Which mechanism-based conclusion is best?

A. Small intestinal mucosal absorptive capacity is preserved; fat malabsorption is most consistent with intraluminal pancreatic maldigestion.
B. Normal D-xylose proves celiac disease because D-xylose requires villous atrophy to be absorbed.
C. Low fecal elastase indicates bile acid diarrhea, not pancreatic disease.
D. Steatorrhea with normal D-xylose must be caused by intestinal lymphangiectasia.
E. Pancreatic calcification invalidates all stool tests.

Answer: A

Mechanism pearl: **D-xylose** absorption tests small-intestinal mucosal uptake independent of pancreatic enzymes and bile acids. Normal D-xylose with low **fecal elastase** points to **pancreatic maldigestion**.

26. D-xylose false-positive trap

A patient with advanced chronic kidney disease has suspected malabsorption. After D-xylose ingestion, urinary D-xylose excretion is low, but the 1-hour blood level is acceptable and duodenal biopsies are normal.

What is the best explanation?

A. Low urinary D-xylose always proves celiac disease.
B. Renal dysfunction can falsely reduce urinary D-xylose excretion despite adequate intestinal absorption.
C. Pancreatic insufficiency causes falsely low serum D-xylose.
D. D-xylose is absorbed only in the terminal ileum, so kidney disease is irrelevant.
E. Bacterial overgrowth prevents all blood absorption of D-xylose.

Answer: B

Mechanism pearl: D-xylose interpretation must account for **renal function**, because urinary recovery depends on renal excretion and can be falsely low in renal impairment.

27. Fecal osmotic gap: mechanism and calculation

A 44-year-old man has watery diarrhea that stops during fasting. Stool sodium is 20 mmol/L and stool potassium is 25 mmol/L. Stool osmolality is not contaminated. He uses sugar-free candies.

Which interpretation is most accurate?

A. The osmotic gap is low, proving secretory diarrhea.
B. The osmotic gap is 90 mOsm/kg, proving inflammatory diarrhea.
C. The osmotic gap is 200 mOsm/kg, supporting osmotic diarrhea from unmeasured poorly absorbed solutes.
D. The osmotic gap cannot be calculated without stool chloride.
E. Fasting cessation of diarrhea excludes osmotic diarrhea.

Answer: C

Mechanism pearl: Fecal osmotic gap = **290 - 2 x (stool Na + stool K)**. Here: 290 - 2(45) = **200**, supporting **osmotic diarrhea** from unmeasured osmoles.

28. Secretory diarrhea physiology

A 59-year-old woman has 8 watery stools/day including nocturnal diarrhea. Symptoms persist during fasting. Stool sodium is 85 mmol/L and potassium is 50 mmol/L.

Which mechanism best fits this stool profile?

A. Ingestion of magnesium-containing laxatives producing electrolyte-poor stool.
B. Carbohydrate malabsorption with low stool sodium and high stool osmotic gap.
C. Normal colonic absorption with retained dietary osmoles only.
D. Fat malabsorption with no fluid-electrolyte component.
E. Electrolyte-rich stool from impaired electrolyte absorption or active secretion, producing a low osmotic gap.

Answer: E

Mechanism pearl: **Secretory diarrhea** produces electrolyte-rich stool, a **low fecal osmotic gap**, nocturnal symptoms, and persistence with fasting.

29. Stool osmolality contamination trap

A patient with chronic diarrhea has stool sodium 8 mmol/L, potassium 12 mmol/L, and measured stool osmolality of 120 mOsm/kg. The calculated osmotic gap seems very high.

Which interpretation is safest?

A. This proves congenital chloridorrhea.
B. Measured stool osmolality well below plasma suggests dilution by water or hypotonic urine, invalidating the osmotic gap.
C. A measured osmolality of 120 is typical of secretory diarrhea.
D. Low stool sodium confirms VIPoma.
E. The test proves bile acid diarrhea.

Answer: B

Mechanism pearl: Colonic fluid usually equilibrates near plasma osmolality. Very low measured **stool osmolality** suggests **dilution/contamination**, which falsely elevates the calculated osmotic gap.

30. Surreptitious laxative ingestion: diagnostic discipline

A 26-year-old woman has recurrent admissions for severe watery diarrhea, hypokalemia, and weight preoccupation. Stool laxative screen is positive once for stimulant laxatives.

What is the most appropriate interpretation?

A. Confront immediately because one positive screen is definitive and never needs confirmation.
B. Ignore the result because laxatives cannot cause chronic diarrhea.
C. Diagnose VIPoma because laxative screens are always false positives.

D. Repeat confirmatory testing on another stool/urine sample before confrontation and arrange appropriate psychological support.

E. Treat with cholestyramine because all factitious diarrhea is bile acid mediated.

Answer: D

Mechanism pearl: Testing for **surreptitious laxative ingestion** is error-prone. A positive result should be **confirmed** before confrontation; management often requires psychiatric/psychological support.

31. Magnesium laxative: osmotic physiology

A patient has watery diarrhea that resolves in hospital. Fecal osmotic gap is high and stool magnesium concentration is markedly elevated.

Which mechanism is most likely?

A. Poorly absorbed magnesium salts retain water intraluminally as unmeasured osmoles.

B. VIP-mediated chloride secretion through cAMP.

C. Bile acids reaching the colon after ileal resection.

D. Bacterial bile salt deconjugation with low stool magnesium.

E. Clonal intraepithelial lymphocytes causing lymphoma.

Answer: A

Mechanism pearl: Magnesium-containing laxatives cause **osmotic diarrhea** by retaining water in the lumen and increasing the **osmotic gap**.

32. Carbohydrate malabsorption and breath testing

A patient develops bloating and diarrhea after milk. Lactose hydrogen breath test shows a >20 ppm rise, but she had antibiotics last week and also has suspected SIBO.

Which mechanistic caveat is most important?

A. Hydrogen breath testing does not require bacterial fermentation.

B. SIBO can cause false-positive early hydrogen rises, and recent antibiotics can cause false-negative results by suppressing fermenting bacteria.

C. A positive breath test excludes lactase deficiency.

D. Lactose malabsorption causes low osmotic gap secretory diarrhea.

E. Methane production proves pancreatic insufficiency.

Answer: B

Mechanism pearl: Hydrogen breath tests depend on **microbial fermentation** of unabsorbed carbohydrate. **SIBO** can create early false positives; **antibiotics** may suppress hydrogen production.

33. Interpreting quantitative fecal fat

A patient on laxatives has stool fat excretion of 9 g/day during severe diarrhea. Another patient has 24 g/day despite controlled stool volume.

Which interpretation is most accurate?

A. Any value above 7 g/day is equally specific for malabsorption.

B. Fecal fat is irrelevant because steatorrhea can only be diagnosed visually.

C. Mild elevations can occur with diarrhea itself, whereas higher values strongly support defective fat absorption or digestion.

D. Fecal fat between 7 and 14 g/day proves pancreatic cancer.

E. A Sudan stain is always more accurate than timed fecal fat collection.

Answer: C

Mechanism pearl: Timed fecal fat is useful, but mild **steatorrhea** may occur from diarrhea-induced transit. Markedly elevated fat output is more specific for true maldigestion/malabsorption.

34. Zollinger-Ellison malabsorption mechanism

A 45-year-old man has severe refractory peptic ulcers, diarrhea, steatorrhea, high fasting gastrin, and gastric pH 1.0. Pancreatic imaging is normal.

Which mechanism best explains steatorrhea?

A. Gastrin directly blocks ileal bile acid transporters.

B. High acid destroys enterocyte HLA-DQ2 molecules.

C. Massive acid secretion inactivates pancreatic lipase, impairs bile salt function, and injures proximal small bowel mucosa.

D. Gastrinoma causes lymphatic rupture and chylous ascites.

E. Gastrin increases intestinal methanogen growth, causing fat malabsorption.

Answer: C

Mechanism pearl: In **Zollinger-Ellison syndrome**, severe acid load can inactivate **pancreatic lipase**, impair **bile salt** function, and injure duodenal mucosa, causing diarrhea and steatorrhea.

35. VIPoma and receptor signaling

A 52-year-old woman has 4 L/day watery diarrhea, hypokalemia, dehydration, and achlorhydria. Diarrhea persists during fasting. Imaging reveals a pancreatic tail mass.

Which signaling mechanism best explains the diarrhea?

A. Serotonin-mediated fibrosis of the ileocecal valve.
B. Somatostatin receptor activation inhibiting pancreatic bicarbonate.
C. Aldosterone receptor blockade in colonic epithelial cells.
D. VIP-mediated activation of adenylate cyclase/cAMP pathways driving intestinal electrolyte and water secretion.
E. tTG-mediated gliadin deamidation causing villous atrophy.

Answer: D

Mechanism pearl: VIPoma causes secretory diarrhea via **VIP receptor** signaling and **cAMP-mediated chloride/water secretion**, leading to watery diarrhea and hypokalemia.

36. Somatostatinoma: comparative hormone pharmacology

A patient has diabetes, gallstones, steatorrhea, weight loss, and a pancreatic neuroendocrine tumor producing somatostatin.

Which mechanism best explains the syndrome?

A. Somatostatin inhibits insulin, cholecystokinin-mediated gallbladder contraction, and pancreatic exocrine secretion.
B. Somatostatin increases ileal bile acid uptake and prevents gallstone formation.
C. Somatostatin activates CFTR directly and produces high-volume chloride diarrhea.
D. Somatostatin deamidates gliadin and activates HLA-DQ8.
E. Somatostatin induces chylomicron assembly failure.

Answer: A

Mechanism pearl: Somatostatinoma is a hormone-inhibition syndrome: impaired **insulin** secretion, reduced **CCK/gallbladder** activity, and reduced **pancreatic exocrine** output explain diabetes, gallstones, and steatorrhea.

37. Microscopic colitis: biopsy despite normal colonoscopy

A 67-year-old woman has 8 months of nonbloody watery diarrhea, urgency, nocturnal stools, and weight loss. Colonoscopy shows normal mucosa. She uses lansoprazole and NSAIDs.

Which diagnostic step is most mechanism-based?

A. Diagnose IBS-D because normal mucosa excludes organic disease.
B. Perform capsule endoscopy as the first diagnostic test because microscopic colitis is a small-bowel disease.
C. Obtain multiple biopsies from both right and left colon to detect lymphocytic or collagenous colitis.
D. Measure stool elastase because normal colonoscopy proves pancreatic insufficiency.
E. Start gluten-free diet without biopsy because microscopic colitis is always celiac disease.

Answer: C

Mechanism pearl: Microscopic colitis causes chronic watery diarrhea with **normal or near-normal colonoscopy**. Diagnosis requires **colonic biopsies**, including right and left colon.

38. Collagenous versus lymphocytic colitis histology

A patient with chronic watery diarrhea has normal colonoscopy. Biopsies show surface epithelial injury, lamina propria inflammation, and a thickened subepithelial collagen band >10 microns.

Which mechanism-based diagnosis fits best?

A. Lymphocytic colitis, because collagen deposition excludes microscopic colitis.
B. Collagenous colitis, a microscopic colitis subtype with epithelial injury and subepithelial collagen deposition.
C. Celiac disease type II, because collagen bands are clonal T-cell markers.
D. Bile acid diarrhea, because histology is always diagnostic.
E. Whipple disease, because PAS-positive macrophages form collagen bands.

Answer: B

Mechanism pearl: Collagenous colitis is defined by a thickened **subepithelial collagen band** with chronic mucosal inflammation and epithelial injury.

39. Microscopic colitis and celiac overlap

A woman with lymphocytic colitis improves only partially with budesonide and has iron deficiency and osteopenia. The colon biopsy shows increased intraepithelial lymphocytes without a collagen band.

Which associated disease should be actively excluded?

A. Celiac disease, because lymphocytic colitis has a recognized association with gluten-sensitive enteropathy.
B. Wilson disease, because colonic IELs bind copper.
C. VIPoma, because microscopic colitis always indicates endocrine diarrhea.

D. Abetalipoproteinemia, because lymphocytic colitis causes acanthocytosis.

E. Achalasia, because colonic IELs destroy myenteric neurons.

Answer: A

Mechanism pearl: Lymphocytic colitis has clinically important overlap with **celiac disease**; malabsorptive clues should prompt celiac evaluation.

40. Budesonide in microscopic colitis

A 64-year-old woman with biopsy-proven collagenous colitis has severe watery diarrhea. Budesonide is chosen over systemic prednisolone.

Which pharmacologic property best supports this choice?

A. Irreversible CFTR blockade in colonic crypt cells.

B. Bile acid sequestration with no steroid receptor activity.

C. Selective methane suppression in archaea.

D. High topical glucocorticoid activity in the gut with extensive first-pass hepatic metabolism limiting systemic exposure.

E. Direct inhibition of tTG-IgA binding.

Answer: D

Mechanism pearl: Budesonide provides local **glucocorticoid receptor** activity with high first-pass metabolism, making it rational for microscopic colitis induction therapy.

41. Brainerd diarrhea versus inflammatory colitis

Several members of a community develop abrupt-onset severe watery diarrhea after a shared food exposure. Cultures remain negative, symptoms persist for many months, and no organism is identified.

Which interpretation best fits the syndrome described in uploaded diarrhea sources?

A. Classic VIPoma because community outbreaks are typical of neuroendocrine tumors.

B. Celiac crisis because all patients have HLA-DQ2.

C. Short bowel syndrome because diarrhea lasting months requires resection.

D. Munchausen by proxy because epidemic diarrhea is always factitious.

E. Epidemic idiopathic secretory diarrhea, also known as Brainerd diarrhea.

Answer: E

Mechanism pearl: Brainerd diarrhea is an epidemic form of chronic idiopathic secretory diarrhea with abrupt onset, prolonged course, and no consistently identified pathogen.

42. Medication-induced diarrhea: not all chronic diarrhea is IBS

A 73-year-old man develops chronic watery diarrhea after medication changes. Colonoscopy is normal. His drug list includes magnesium antacids, acarbose, antibiotics, olmesartan, lansoprazole, and NSAIDs.

Which reasoning strategy is best?

A. The medication list is irrelevant once colonoscopy is normal.

B. Only antibiotics can cause chronic diarrhea; the other drugs should be ignored.

C. A careful drug review is essential because multiple common and overlooked medications can cause diarrhea or microscopic colitis-like presentations.

D. Olmesartan prevents enteropathy and excludes drug-induced diarrhea.

E. Magnesium antacids cause secretory low-gap diarrhea only.

Answer: C

Mechanism pearl: A difficult chronic diarrhea workup requires **medication review**. Drugs can cause osmotic diarrhea, secretory diarrhea, microbiome disruption, or **microscopic colitis** associations.

43. Whipple disease: systemic macrophage infection

A 56-year-old man has years of migratory arthralgia followed by weight loss, diarrhea, steatorrhea, hyperpigmentation, lymphadenopathy, and cognitive changes. Duodenal biopsy shows PAS-positive macrophages; Ziehl-Neelsen stain is negative.

Which mechanism best explains the disease?

A. HLA-DQ2-mediated gluten presentation causing isolated mucosal CD4 activation.

B. Systemic Tropheryma whipplei infection with macrophage-laden small-bowel mucosal infiltration and possible lymphatic obstruction.

C. Methane-producing archaea causing constipation and low folate.

D. Bile acid sequestration causing colonocyte starvation.

E. Pancreatic lipase deficiency due to duct obstruction.

Answer: B

Mechanism pearl: Whipple disease is a systemic infection due to **Tropheryma whipplei**, classically with **PAS-positive macrophages** in small bowel and extraintestinal disease.

44. Whipple therapy and occult CNS risk

A patient with confirmed Whipple disease improves rapidly on antibiotics. The team asks why treatment regimens should consider blood-brain barrier penetration even without neurologic symptoms.

Which answer is most mechanism-based?

A. The organism is always confined to the duodenal lumen and never relapses.
B. PAS-positive macrophages are resistant to all systemic antibiotics.
C. CNS disease may be occult or develop later, so regimens should cover possible central nervous system involvement.
D. Antibiotics are used only to treat bacterial overgrowth secondary to Whipple disease.
E. CNS penetration prevents celiac-associated lymphoma.

Answer: C

Mechanism pearl: Whipple disease can involve the **central nervous system** even when GI features dominate. Therapy must account for potential occult CNS infection and relapse risk.

45. Giardia and diagnostic efficiency

A backpacker has chronic bloating, foul stools, weight loss, and intermittent diarrhea. Ova and parasite microscopy is repeatedly negative, but suspicion remains high.

Which diagnostic principle is best supported by the uploaded diarrhea sources?

A. Giardia is best diagnosed by stool sodium and potassium only.
B. Microscopy is always more efficient than antigen testing for Giardia.
C. Giardia antigen testing is more efficient than routine microscopy when clinical suspicion persists.
D. Giardia causes low IgA and should be diagnosed by HLA-DQ8 testing.
E. Giardia is excluded by normal colonoscopy.

Answer: C

Mechanism pearl: For chronic diarrhea, **Giardia antigen testing** can be more efficient than microscopy and should be considered when malabsorptive symptoms persist.

46. Abetalipoproteinemia: chylomicron assembly failure

A teenager has lifelong fat malabsorption, failure to thrive, acanthocytic red cells, very low LDL cholesterol, retinitis pigmentosa, and progressive neurologic signs from vitamin E deficiency.

Which molecular mechanism is most likely?

A. Defective terminal ileal bile acid transporter causing isolated bile acid diarrhea.
B. Mitochondrial trifunctional protein deficiency causing acute fatty liver of pregnancy.
C. tTG-mediated deamidation of dietary gliadin.
D. Failure of apolipoprotein B-containing lipoprotein assembly and chylomicron export from enterocytes.
E. VIP receptor overactivation causing electrolyte-rich diarrhea.

Answer: D

Mechanism pearl: **Abetalipoproteinemia** impairs apoB-containing lipoprotein assembly, so enterocytes cannot export **chylomicrons**, causing fat malabsorption and fat-soluble vitamin deficiency.

47. CVID/hypogammaglobulinemia and celiac-like enteropathy

A 38-year-old man has recurrent sinopulmonary infections, chronic diarrhea, villous atrophy, negative celiac serology, and low IgG/IgA/IgM. He does not improve with gluten withdrawal.

Which mechanism best explains the celiac-like presentation?

A. Congenital chloride transporter activation causing isolated high stool chloride.
B. Hypogammaglobulinemia-associated enteropathy with impaired mucosal immunity, often mimicking celiac disease and predisposing to infections/SIBO.
C. Pancreatic neuroendocrine VIP secretion.
D. Terminal ileal peptide YY excess causing slow transit.
E. Surreptitious magnesium ingestion causing villous atrophy.

Answer: B

Mechanism pearl: **CVID/hypogammaglobulinemia** can cause celiac-like villous atrophy with negative serology and impaired mucosal immunity, and may coexist with **SIBO** or infections.

48. Autoimmune enteropathy versus celiac disease

An adult with severe refractory diarrhea has villous atrophy, negative celiac serology, negative HLA-DQ2/DQ8, anti-enterocyte antibodies, and no response to gluten withdrawal.

Which mechanism-based diagnosis should be favored?

A. Autoimmune enteropathy due to immune-mediated epithelial injury rather than gluten-HLA-driven celiac disease.

B. Classic celiac disease because villous atrophy alone is diagnostic.

C. Bile acid diarrhea because HLA testing is negative.

D. Lactase deficiency because anti-enterocyte antibodies are diagnostic of lactose malabsorption.

E. VIPoma because all seronegative enteropathies are endocrine.

Answer: A

Mechanism pearl: Seronegative villous atrophy requires a broad differential. Negative **HLA-DQ2/DQ8** and lack of gluten response argue against celiac disease and support **autoimmune enteropathy** in the right context.

49. Fatty diarrhea: combined mechanisms in SIBO and short bowel

A patient with short bowel syndrome and a blind segment has steatorrhea. His consultant says one mechanism is never enough in malabsorption.

Which combined mechanism is most plausible?

A. Reduced surface area, bile acid pool depletion, bacterial bile salt deconjugation, and brush-border injury may all contribute simultaneously.

B. Only pancreatic lipase deficiency can produce steatorrhea, regardless of anatomy.

C. Only mucosal villous atrophy can produce fat malabsorption.

D. Bile acids reaching the colon always improve fat absorption.

E. Lymphatic obstruction prevents protein loss but increases fat absorption.

Answer: A

Mechanism pearl: Complex malabsorption often combines **intraluminal**, **mucosal**, and **postmucosal** mechanisms. In **SBS/SIBO**, surface loss, bile acid depletion, and bacterial deconjugation may coexist.

50. Most difficult integrative diarrhea localization

A 64-year-old woman has chronic watery diarrhea including nocturnal stools. Stool osmotic gap is 18 mOsm/kg, fecal fat is negative, colonoscopy is normal, random biopsies show no microscopic colitis, celiac serology is negative with normal IgA, and ileocolonoscopy shows a subtle ileal stricture with prior cholecystectomy. A trial of cholestyramine markedly improves symptoms.

Which final mechanism best explains the response?

A. Osmotic diarrhea from unabsorbed sorbitol.

B. Pancreatic exocrine insufficiency causing fat maldigestion.

C. Functional diarrhea because nocturnal stools are typical.

D. Bile acid-mediated colonic secretion from impaired ileal bile acid reclamation and altered enterohepatic cycling.

E. Refractory celiac disease type II with clonal IELs.

Answer: D

Mechanism pearl: Low osmotic gap, nocturnal watery stools, negative fat, and response to sequestration support **bile acid diarrhea**, especially with ileal disease or post-cholecystectomy physiology.

Source-map themes used

• Celiac disease: HLA-DQ2/DQ8 exclusion logic, tTG-mediated deamidation, IgA deficiency, patchy biopsy disease, refractory celiac disease and clonal IELs.

• SIBO: motility/stasis, hypochlorhydria, bile salt deconjugation, B12 consumption with folate production, breath testing limitations, aspirate culture limitations.

• Diarrhea: osmotic versus secretory physiology, fecal osmotic gap, stool contamination traps, medication/laxative diarrhea, microscopic colitis and bile acid diarrhea.

• Malabsorption: intraluminal digestion versus mucosal absorption versus postmucosal transport, short bowel syndrome, D-lactic acidosis, enteric hyperoxaluria, lymphangiectasia, Whipple disease, and abetalipoproteinemia.