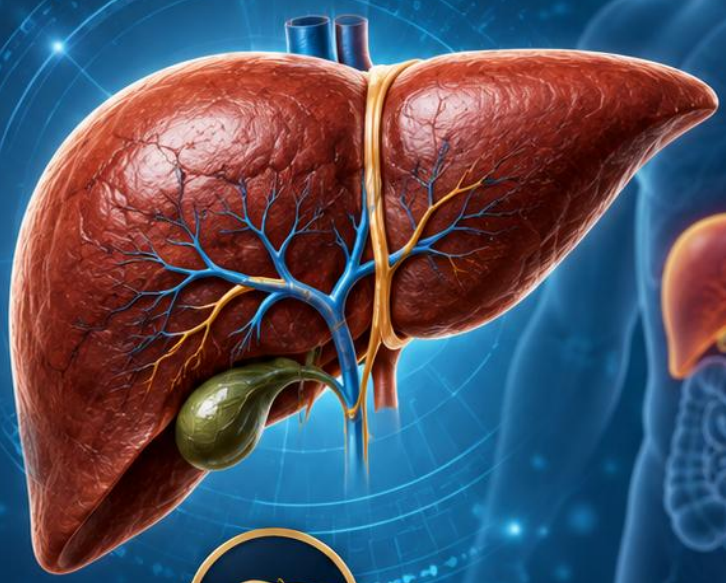
ADVANCED HEPATOLOGY

MECHANISM-BASED MCQ EXAMINATION



- MECHANISM FOCUSED
- EVIDENCE BASED
- CLINICALLY RELEVANT
- EXAM ORIENTED

Done by

Dr.Omar Reda

GE and hepatology consultant

Advanced Hepatology MCQ Exam – prepared by Dr. Omer Reda GE and hepatology consultant

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..

Advanced Hepatology Mechanism-Based MCQ Examination

100 direct/short case scenarios + 50 moderate-to-long case scenarios

Original consultant-level questions constructed from the uploaded hepatology and gastroenterology/hepatology references only. The emphasis is mechanism-based reasoning: receptor pharmacology, intracellular signaling, immune pathways, biomarker biology, comparative pharmacology, translational hepatology, and pathophysiology. Correct answers are randomized across A-E. Key mechanism terms are bolded and colored.

Source basis used for construction and validation: Yamada's Textbook of Gastroenterology 7E; Sleisenger & Fordtran 11E; Sherlock's Diseases of the Liver; Handbook of Liver Disease; CURRENT Diagnosis & Treatment Gastroenterology, Hepatology & Endoscopy; Gastrointestinal and Liver Secrets; Practical Hepatology; Practical Gastroenterology and Hepatology: Liver and Biliary Disease; Textbook of Clinical Gastroenterology and Hepatology; Zakim and Boyer's Hepatology; Mayo/Brigham board review sources; ACG uploaded source file.

Section A - 100 Direct and Short Case Scenario MCQs

Question 1. HRS; terlipressin; V1

A 58-year-old man with decompensated cirrhosis has rising creatinine despite albumin expansion and diuretic withdrawal. Terlipressin is started.

Lead-in: Which receptor-level action best explains the intended renal improvement?

A. V1 receptor-mediated splanchnic vasoconstriction increases effective arterial blood volume and reduces renal vasoconstrictor drive
B. Beta-2 receptor blockade selectively dilates the renal afferent arteriole
C. V2 receptor antagonism produces aquaresis and directly increases GFR
D. Dopamine D1 agonism increases renal cortical blood flow
E. Endothelin receptor agonism reduces intrarenal vascular resistance
Answer: A | Mechanism pearl: HRS is a functional renal vasoconstrictive state driven by severe splanchnic vasodilatation; V1 agonism reverses the circulatory trigger rather than treating intrinsic renal disease.

Question 2. HRS; midodrine; octreotide

A cirrhotic patient with refractory ascites is treated with midodrine plus octreotide while awaiting transplant evaluation.

Lead-in: Which combination of mechanisms best explains this regimen?

A. Alpha-1 agonism raises systemic vascular tone while somatostatin receptor activation reduces splanchnic vasodilatory flow
B. Direct renal prostaglandin inhibition plus endothelin blockade improves filtration
C. FXR activation reduces portal pressure while PPAR-alpha activation increases albumin synthesis
D. Dopamine agonism and muscarinic blockade increase renal sodium excretion
E. V2 blockade increases free-water excretion while beta-1 blockade reduces renin
Answer: A | Mechanism pearl: Midodrine supports arterial pressure; octreotide reduces splanchnic inflow. The physiologic target is effective arterial underfilling.

Question 3. hyponatremia; AVP; V2

A woman with tense ascites has severe hyponatremia with concentrated urine despite low serum osmolality.

Lead-in: What is the dominant signaling abnormality?

A. Non-osmotic AVP release causing V2 receptor-mediated aquaporin insertion and water retention
B. Direct bilirubin toxicity causing nephrogenic diabetes insipidus
C. Excess atrial natriuretic peptide causing free-water retention
D. Primary adrenal aldosterone failure causing renal salt wasting
E. Suppressed RAAS causing failure of distal sodium delivery
Answer: A | Mechanism pearl: Cirrhotic hyponatremia is water retention from AVP excess; sodium restriction alone does not address the water-handling defect.

Question 4. tolvaptan; V2; aquaresis

A patient with cirrhosis receives tolvaptan for severe dilutional hyponatremia under close monitoring.

Lead-in: Which mechanism best explains the rise in serum sodium?

A. Mineralocorticoid receptor blockade reduces potassium loss
B. V1 receptor agonism constricts splanchnic vessels
C. Selective V2 receptor antagonism reduces collecting-duct aquaporin-2 insertion and promotes aquaresis
D. FXR agonism suppresses bile acid synthesis
E. Loop diuretic action in the thick ascending limb increases medullary tonicity
Answer: C | Mechanism pearl: Vaptans produce electrolyte-sparing water excretion; overrapid correction is the major clinical danger.

Question 5. portal hypertension; propranolol

A cirrhotic man with medium esophageal varices is started on propranolol.

Lead-in: Which hemodynamic mechanism is most important?

A. Selective beta-2 agonism decreases azygos flow
B. Alpha-1 blockade increases intrahepatic sinusoidal compliance
C. Beta-1 blockade lowers cardiac output and beta-2 blockade permits splanchnic vasoconstriction
D. V1 blockade reduces portal venous inflow
E. Inhibition of hepatic stellate-cell TGF-beta signaling rapidly reverses fibrosis
Answer: C | Mechanism pearl: Nonselective beta-blockers reduce portal inflow through combined cardiac and splanchnic effects.

Question 6. carvedilol; alpha-1; portal hypertension

A patient with compensated cirrhosis and varices is switched from propranolol to carvedilol.

Lead-in: Which added receptor action explains stronger portal-pressure reduction?

A. D2 antagonism increases gastric emptying and lowers portal flow
B. **Alpha-1** antagonism reduces intrahepatic and systemic vascular resistance in addition to nonselective beta-blockade
C. **FXR** antagonism reduces portal venous inflow
D. V1 agonism increases effective arterial volume
E. GABA-B agonism decreases transient LES relaxations
Answer: B | Mechanism pearl: Carvedilol combines nonselective beta-blockade with **alpha-1** blockade, often lowering **HVPG** more than propranolol.

Question 7. variceal bleeding; octreotide

An actively bleeding variceal patient receives **octreotide** before endoscopy.

Lead-in: What is the most appropriate mechanism?

A. Blockade of **VEGF**-driven angiogenesis within minutes
B. Direct inhibition of **CYP2E1**-dependent **oxidative stress**
C. **Somatostatin** receptor activation reduces splanchnic vasodilatory peptide release and portal venous inflow
D. Direct fibrin cross-linking at the variceal rupture point
E. Selective V2 antagonism causing aquaresis
Answer: C | Mechanism pearl: Octreotide is vasoactive source-control support; it does not replace endoscopic ligation.

Question 8. portal hypertension; eNOS; stellate cell

A trial drug in **portal hypertension** increases hepatic endothelial **nitric oxide** bioavailability while reducing stellate-cell contraction.

Lead-in: Which pathophysiologic defect is it targeting?

A. Direct cytopathic infection of sinusoidal endothelial cells
B. Purely fixed collagen scarring without any dynamic component
C. Primary renal afferent arteriolar thrombosis
D. Autoimmune destruction of portal-vein smooth muscle
E. Dynamic intrahepatic resistance from endothelial dysfunction and activated contractile **stellate cells**
Answer: E | Mechanism pearl: Portal pressure reflects flow and resistance; resistance includes fixed fibrosis and dynamic sinusoidal vasoconstriction.

Question 9. TIPS; HE; ammonia

A cirrhotic patient with refractory ascites improves after **TIPS** but develops confusion.

Lead-in: Which mechanism explains the new complication?

A. Portosystemic shunting bypasses hepatic **ammonia** extraction and increases neurotoxin delivery to brain
B. **TIPS** blocks intestinal **ammonia** production directly
C. **TIPS** activates **BSEP** and raises serum bile acids
D. **TIPS** causes anti-GABA antibody production
E. **TIPS** increases hepatic urea-cycle activity causing excess **glutamine** depletion
Answer: A | Mechanism pearl: TIPS relieves portal pressure but increases shunting, making HE a predictable risk.

Question 10. HE; ammonia; astrocyte

A patient with cirrhosis has confusion after a GI bleed. **Ammonia** rises and MRI suggests cerebral edema.

Lead-in: Which cellular event best explains **ammonia**-related brain swelling?

A. **GABA-A** receptor loss produces excitotoxic necrosis
B. Neuronal heme oxygenase converts **ammonia** to bilirubin
C. Astrocytic **glutamine** accumulation after **ammonia** detoxification by **glutamine** synthetase increases osmotic stress
D. Endothelial **cccDNA** formation induces vasogenic edema
E. Microglia conjugate **ammonia** with bile acids causing demyelination
Answer: C | Mechanism pearl: The brain lacks a urea cycle; **astrocyte**s convert **ammonia** to **glutamine**, causing osmotic swelling.

Question 11. HE; GABA-A; flumazenil

A sedated cirrhotic patient transiently wakes after flumazenil.

Lead-in: Which mechanism is most consistent with this observation?

A. Antagonism at the benzodiazepine site of the **GABA-A** receptor complex reduces excessive inhibitory tone
B. Direct restoration of hepatocyte urea-cycle flux
C. Activation of **NMDA** receptors reverses **manganese** deposition
D. Inhibition of **ammonia** production by gut urease organisms
E. **V2 receptor** blockade reduces **astrocyte** swelling

Answer: A | Mechanism pearl: Flumazenil supports the concept that GABAergic/neurosteroid tone contributes to HE in selected patients.

Question 12. HE; TSPO; neurosteroids

A molecular PET ligand shows increased **TSPO** binding in the brains of patients with hepatic coma.

Lead-in: What does this imply mechanistically?

A. **Mitochondrial** neuroglial **TSPO** activation promotes neurosteroid synthesis that potentiates **GABA-A** signaling
B. **TSPO** blockade is equivalent to **lactulose** acidification
C. **TSPO** identifies portal-vein thrombosis in the basal ganglia
D. **TSPO** activation increases bile-acid export by **BSEP** in **astrocyte**s
E. **TSPO** marks **HBV cccDNA** formation in neurons
Answer: A | Mechanism pearl: HE involves not only **ammonia** but altered neurotransmission; **TSPO**-linked **neurosteroids** can enhance **GABA-A** inhibition.

Question 13. lactulose; HE

A patient with recurrent HE improves on **lactulose** but develops diarrhea when overtreated.

Lead-in: Which mechanism explains **lactulose** benefit?

A. V1-mediated splanchnic vasoconstriction
B. Colonic acidification and catharsis reduce absorbable **ammonia** and nitrogenous substrate
C. Activation of hepatic **mitochondrial** beta-oxidation
D. Selective killing of all urease-positive bacteria by systemic absorption
E. Direct inhibition of CNS **GABA-A** receptors
Answer: B | Mechanism pearl: Lactulose traps **ammonia** as ammonium and accelerates nitrogen elimination; excessive dosing causes dehydration.

Question 14. rifaximin; microbiota; HE

A cirrhotic patient remains encephalopathic despite **lactulose** and receives **rifaximin**.

Lead-in: What distinguishes **rifaximin** mechanistically?

A. Systemic aminoglycoside nephrotoxicity as the intended action
B. Poorly absorbed gut antibiotic effect that modifies **ammonia**-producing intestinal microbiota
C. **FXR** agonism increasing **BSEP** expression
D. Direct astrocytic **glutamine** synthetase inhibition
E. Selective **V2 receptor** antagonism
Answer: B | Mechanism pearl: Rifaximin acts mainly within the intestinal lumen and is used as add-on prevention after overt HE.

Question 15. BCAA; sarcopenia; HE

A patient with sarcopenic cirrhosis has recurrent minimal HE. Oral **BCAA** supplementation is considered.

Lead-in: Which mechanism is most plausible?

A. **BCAA**s support peripheral **ammonia** detoxification and compete with aromatic amino acids for brain transport
B. **BCAA**s antagonize **V1 receptor**s in splanchnic vessels
C. **BCAA**s directly bind **GABA-A** receptor benzodiazepine sites
D. **BCAA**s inhibit **BSEP** to increase bile acid excretion
E. **BCAA**s induce **CYP2E1** to clear **ammonia**
Answer: A | Mechanism pearl: Skeletal muscle is an auxiliary **ammonia**-detoxifying organ; sarcopenia worsens HE vulnerability.

Question 16. LOLA; ammonia

A research protocol gives L-ornithine L-aspartate to lower **ammonia** in cirrhosis.

Lead-in: Which biochemical effect is intended?

A. Activation of **V1 receptor**s in the splanchnic bed
B. Provision of substrates for urea-cycle and **glutamine**-synthesis pathways that detoxify **ammonia**
C. Inhibition of **GABA-A** receptor chloride channels
D. Binding of anti-**HCV** IgG cryoprecipitates
E. Blockade of intestinal sodium-bile acid cotransport
Answer: B | Mechanism pearl: LOLA targets nitrogen disposal rather than acid suppression or portal-pressure reduction.

Question 17. HCV; cryoglobulinemia; MPGN

A man with chronic **HCV** develops palpable purpura, neuropathy, low **C4**, RF positivity, and **MPGN**.

Lead-in: Which mechanism best explains the syndrome?

A. Primary complement C3 convertase genetic deficiency
B. CD8 T-cell molecular mimicry against basement membrane collagen IV
C. Direct **HCV** cytolysis of vascular endothelial cells
D. **HCV**-driven B-cell expansion produces **IgM rheumatoid factor** that complexes with anti-**HCV** IgG and deposits in small vessels
E. Monoclonal IgG plasma-cell hyperviscosity alone
Answer: D | Mechanism pearl: **HCV** mixed **cryoglobulinemia** is immune-complex disease with low **C4** and **MPGN**, not direct endothelial infection.

Question 18. HCV; cryoglobulinemia; B cell

A patient with **HCV**-associated cryoglobulinemic vasculitis improves after viral eradication.

Lead-in: Which principle explains the parallel fall in cryocrit and symptoms?

A. Removal of the chronic antigenic B-cell stimulus reduces pathogenic immune-complex production
B. Viral eradication induces renal prostaglandin synthesis
C. **DAA**s directly dissolve complement **C4** deposits
D. Ribosomal RNA inhibition suppresses endothelial necrosis
E. **Protease inhibitor**s deplete all plasma cells irreversibly
Answer: A | Mechanism pearl: The driver is persistent **HCV** antigenic stimulation; treating the virus treats the **immune complex** trigger.

Question 19. HBV; cccDNA

A patient with chronic **HBV** starts entecavir and achieves undetectable serum **HBV** DNA, but HBsAg persists.

Lead-in: Which viral reservoir explains incomplete sterilizing cure?

A. HBsAg is produced by host **albumin** mRNA splicing
B. **HBV** becomes **HDV** and uses **HCV** **NS5B** polymerase
C. **HBV** hides exclusively as cytoplasmic double-stranded RNA
D. Stable nuclear **cccDNA** and sometimes integrated **HBV** DNA continue viral antigen production
E. **Mitochondrial** RNA replicons persist in **Kupffer cells**
Answer: D | Mechanism pearl: Nucleos(t)ide analogues suppress reverse transcription but do not reliably eliminate **cccDNA**.

Question 20. HBV; tenofovir

A patient receives tenofovir for chronic **HBV**.

Lead-in: Which step of the **HBV** life cycle is directly inhibited?

A. **FXR**/RXR binding to **BSEP** promoter
B. Entry via **CD81** into B lymphocytes
C. **HDV** ribozyme cleavage in the nucleus
D. **NS5A**-mediated membranous-web assembly
E. Reverse transcription of pregenomic RNA by **HBV** polymerase
Answer: E | Mechanism pearl: **HBV** is a DNA virus but replicates through an RNA intermediate; polymerase inhibition suppresses DNA production.

Question 21. HBV reactivation; anti-CD20

A man with resolved **HBV** receives rituximab and develops severe **HBV** reactivation.

Lead-in: Which immune mechanism explains the risk?

A. Rituximab blocks **NTCP** and forces viral escape
B. B-cell depletion impairs humoral immune surveillance against persistent **HBV** templates
C. Rituximab activates **HCV** **NS5A** replication
D. Selective expansion of **Treg**s destroys **cccDNA**
E. Increased **BSEP** expression causes **HBV** entry
Answer: B | Mechanism pearl: Resolved serology does not equal elimination of **HBV**; **anti-CD20** therapy is a high-risk reactivation setting.

Question 22. HDV; HBsAg

A patient with **HBV** is found to have coinfection with hepatitis D.

Lead-in: Which virologic dependency explains **HDV** persistence?

A. **HDV** requires HBsAg envelope supplied by **HBV** for virion assembly and spread
B. **HDV** uses EBV latent membrane protein for entry
C. **HDV** replication requires HAV capsid antigen
D. **HDV** integrates into **mitochondrial** DNA to make envelope protein
E. **HDV** requires **HCV** **NS5B** polymerase
Answer: A | Mechanism pearl: **HDV** is a defective RNA virus; **HBV** surface antigen is required for complete virion formation.

Question 23. HCV; NS5B; sofosbuvir

A patient with HCV genotype infection receives sofosbuvir-based therapy.

Lead-in: Which molecular target is sofosbuvir designed to inhibit?

A. HBV reverse transcriptase
B. NS5A replication-complex scaffolding as a phosphoprotein inhibitor
C. NS3/4A protease active site as a macrocyclic inhibitor
D. Host NTCP bile acid transporter
E. NS5B RNA-dependent RNA polymerase as a nucleotide analogue
Answer: E | Mechanism pearl: Sofosbuvir is an NS5B nucleotide inhibitor; correct DAA class recognition matters for resistance and interactions.

Question 24. HCV; NS5A

A patient with HCV is treated with velpatasvir.

Lead-in: Which mechanism best describes the drug class?

A. V1 agonism increases effective arterial volume
B. CYP2E1 inhibition prevents NAPQI formation
C. BSEP antagonism increases bile acid synthesis
D. NS5A inhibition disrupts replication-complex organization and virion assembly
E. PXR activation increases biliary MRP2
Answer: D | Mechanism pearl: NS5A inhibitors are potent but resistance-prone; they target a multifunctional nonenzymatic replication protein.

Question 25. HCV; protease inhibitor; decompensation

A cirrhotic patient with decompensated Child-Pugh C disease is considered for an HCV protease inhibitor regimen.

Lead-in: What is the key mechanistic concern?

A. Protease inhibitors bind bile acids and worsen steatorrhea
B. Protease inhibitors require normal renal prostaglandins for efficacy
C. Protease inhibitors invariably activate HBV cccDNA
D. Hepatic metabolism and toxicity risk make protease inhibitors unsafe in advanced decompensation
E. Protease inhibitors block lactulose metabolism
Answer: D | Mechanism pearl: NS3/4A protease inhibitor regimens require careful hepatic-function selection.

Question 26. DAA; HBV reactivation

After rapid HCV clearance with DAAs, a patient with occult HBV develops acute hepatitis.

Lead-in: Which mechanism best explains this complication?

A. Rifaximin reduces hepatic B-cell immunity
B. HCV clearance causes acute Wilson-like copper release
C. DAAs mutate HBV polymerase into HCV NS5B
D. Loss of HCV-mediated viral interference permits HBV replication from persistent templates
E. DAAs stimulate bile acid synthesis through CYP7A1
Answer: D | Mechanism pearl: HBV screening before DAA therapy is necessary because HBV may reactivate after HCV suppression.

Question 27. APAP; NAPQI; glutathione

A patient has acetaminophen overdose with very high aminotransferases.

Lead-in: Which early molecular event initiates hepatocyte injury?

A. V2 receptor activation causes hepatocyte swelling
B. BSEP activation causes bile-acid depletion
C. CYP-mediated NAPQI formation depletes glutathione and covalently injures mitochondrial proteins
D. PDC-E2-specific AMA destroys bile ducts
E. IgM rheumatoid factor complexes deposit in sinusoids
Answer: C | Mechanism pearl: APAP injury is dose-related and centered on reactive metabolite formation and mitochondrial oxidative stress.

Question 28. NAC; APAP

A patient presents late after acetaminophen overdose and still receives N-acetylcysteine.

Lead-in: Which mechanism supports NAC use beyond simple early detoxification?

A. V2 antagonism correcting hyponatremia
B. Replenishment of glutathione plus antioxidant and microcirculatory benefits during evolving injury

C. FXR agonism reducing bile acid synthesis
D. Direct inhibition of HBV polymerase
E. Selective blockade of TNF-alpha receptors
Answer: B | Mechanism pearl: NAC provides cysteine for **glutathione** and may improve outcomes even after the classic early window in severe injury.

Question 29. DILI; HLA; hapten

A man taking isoniazid develops severe hepatitis with fever, rash, eosinophilia, and positive immune markers.

Lead-in: Which model best explains idiosyncratic **DILI**?

A. V1-mediated ischemia of the portal vein
B. Predictable direct toxicity proportional to every therapeutic dose
C. Defective **ATP7B** copper excretion in bile
D. Loss of **cccDNA** immune control by **anti-CD20** therapy
E. Reactive drug-protein adducts presented in susceptible **HLA** contexts trigger adaptive immune injury
Answer: E | Mechanism pearl: Many idiosyncratic **DILI** syndromes combine metabolism, **HLA** susceptibility, and adaptive immune activation.

Question 30. mitochondrial DILI; microvesicular steatosis

A drug causes **microvesicular steatosis**, lactic acidosis, and acute liver failure.

Lead-in: Which mechanism is most likely?

A. **BSEP** overexpression with excessive bile flow
B. IgM RF immune-complex deposition
C. **Mitochondrial** beta-oxidation impairment with defective ATP generation
D. Direct **V2 receptor**-mediated water retention
E. Selective **IL-2** transcription blockade
Answer: C | Mechanism pearl: Microvesicular steatosis is a red flag for **mitochondrial** toxicity, not ordinary insulin-resistance steatosis.

Question 31. amiodarone; phospholipidosis

A patient taking amiodarone develops chronic liver injury with phospholipid-laden lysosomes.

Lead-in: Which mechanism is most coherent?

A. Cationic amphiphilic drug accumulation causing phospholipidosis and **mitochondrial** stress
B. Purely immune-complex vasculitis with low **C4**
C. **FGFR4**-mediated suppression of **CYP7A1**
D. Direct activation of **HFE hepcidin** transcription
E. **V1 receptor** agonism in the splanchnic bed
Answer: A | Mechanism pearl: Amiodarone hepatotoxicity reflects tissue accumulation, phospholipidosis, and **mitochondrial** effects.

Question 32. valproate; mitochondria

A patient on valproate develops acute liver failure with **microvesicular steatosis**.

Lead-in: Which mechanism is most implicated?

A. Complement-mediated bile-duct destruction
B. Canalicular **MDR3** overexpression causing biliary phospholipid excess
C. B-cell **CD81** activation with cryoglobulins
D. Dopamine receptor blockade in **stellate cells**
E. **Mitochondrial** fatty-acid oxidation failure causing energy collapse
Answer: E | Mechanism pearl: Valproate is a classic **mitochondrial** hepatotoxin, especially dangerous in vulnerable metabolic states.

Question 33. AIH; T cells; IgG

A woman with autoimmune hepatitis has high IgG, interface hepatitis, and plasma-cell-rich inflammation.

Lead-in: Which immune mechanism best captures **AIH** pathogenesis?

A. Copper transporter failure causing hepatocyte copper retention
B. IgM RF complexes with anti-**HCV** IgG as the dominant mechanism
C. Direct cytopathic viral infection of bile ducts by HAV
D. Loss of tolerance with CD4 helper-cell activation, cytotoxic T-cell injury, plasma-cell IgG production, and impaired regulatory control
E. Primary **BSEP** loss causing bland canalicular cholestasis
Answer: D | Mechanism pearl: AIH is immune-mediated hepatocellular injury; autoantibodies are markers of a broader T-cell/plasma-cell process.

Question 34. AIH; corticosteroids

A patient with AIH improves rapidly after prednisolone.

Lead-in: Which molecular action explains the therapeutic effect?

A. NS5A inhibition of viral assembly
B. Direct chelation of copper from lysosomes
C. V2 blockade at the collecting duct
D. Irreversible depletion of cccDNA
E. Glucocorticoid receptor-mediated transcriptional repression of inflammatory cytokine programs

Answer: E | Mechanism pearl: Steroids broadly suppress immune transcriptional programs; they are not antigen-specific therapy.

Question 35. AIH; azathioprine

Azathioprine is added for steroid-sparing maintenance in AIH.

Lead-in: Which mechanism best explains its role?

A. Direct binding of ammonia in the colon
B. Selective IL-4 receptor alpha blockade
C. Inhibition of calcineurin-dependent IL-2 transcription
D. Conversion to thiopurine metabolites that inhibit purine synthesis and lymphocyte proliferation
E. FXR agonism increasing BSEP expression

Answer: D | Mechanism pearl: Azathioprine targets proliferating lymphocytes; TPMT/NUDT15 status and myelotoxicity matter clinically.

Question 36. AIH; mycophenolate

A woman with AIH cannot tolerate azathioprine and is switched to mycophenolate mofetil.

Lead-in: Which mechanism best explains MMF as an alternative?

A. V1 receptor agonism at mesenteric arteries
B. Copper chelation by thiol exchange
C. Beta-2 blockade of splanchnic vasodilatation
D. Bile acid sequestration in the intestinal lumen
E. Inhibition of inosine monophosphate dehydrogenase limiting guanosine synthesis in lymphocytes

Answer: E | Mechanism pearl: Lymphocytes rely heavily on de novo purine synthesis, making IMPDH inhibition immunosuppressive.

Question 37. tacrolimus; calcineurin; IL-2

Tacrolimus is used after liver transplantation and occasionally in refractory AIH.

Lead-in: Which intracellular pathway is inhibited?

A. NS5B RNA-dependent RNA polymerase
B. Hepcidin binding to ferroportin
C. Calcineurin-dependent NFAT activation and IL-2 transcription in T cells
D. CYP7A1-mediated bile acid synthesis
E. mTOR-dependent protein translation downstream of IL-2 receptor

Answer: C | Mechanism pearl: Calcineurin inhibitors block T-cell activation upstream of IL-2 production.

Question 38. sirolimus; mTOR; HCC

Sirolimus is considered in a transplant recipient with previous HCC.

Lead-in: Which property is mechanistically relevant?

A. NS5A inhibition blocks HBV antigen production
B. Calcineurin inhibition increases IL-2 transcription
C. V1 receptor agonism reduces portal inflow
D. mTOR inhibition reduces T-cell proliferation and may have anti-proliferative/antiangiogenic tumor effects
E. BSEP inhibition increases bile-acid detoxification

Answer: D | Mechanism pearl: mTOR inhibitors act downstream of IL-2 signaling and may be attractive when tumor biology matters.

Question 39. PBC; AMA; PDC-E2

A woman with cholestatic liver tests has AMA positivity and small intrahepatic bile duct injury.

Lead-in: Which autoantigen is classically targeted?

A. TSPO on astrocyte mitochondria
B. E2 component of the pyruvate dehydrogenase complex on biliary epithelial-related mitochondrial antigens
C. ATP7B copper transporter on canaliculi
D. HFE protein on macrophage lysosomes

E. HBV surface antigen on hepatocyte nuclei
Answer: B | Mechanism pearl: PBC is a chronic autoimmune cholangiopathy; **AMA** against **PDC-E2** is the classic serologic clue.

Question 40. PBC; UDCA

A **PBC** patient receives ursodeoxycholic acid and alkaline phosphatase improves.

Lead-in: Which mechanism best describes **UDCA** benefit?

A. V1-mediated splanchnic vasoconstriction
B. Inhibition of **HBV** reverse transcription
C. Copper chelation in hepatocyte lysosomes
D. Hydrophilic bile acid replacement and bicarbonate-rich choleresis protect cholangiocytes from toxic bile acids
E. Direct depletion of autoreactive B cells through CD20 binding
Answer: D | Mechanism pearl: UDCA improves cholestasis and cholangiocyte protection; response predicts prognosis.

Question 41. PBC; OCA; FXR

A **PBC** patient with inadequate **UDCA** response starts obeticholic acid but develops severe pruritus.

Lead-in: Which receptor mechanism explains both efficacy and some adverse effects?

A. D2 receptor blockade increases cholangiocyte secretion
B. **PXR** antagonism suppresses CYP enzymes
C. GABA-B agonism reduces bile acid reuptake
D. **PPAR-alpha** agonism increases **MDR3** only
E. **FXR** agonism suppresses bile acid synthesis and alters transporter expression
Answer: E | Mechanism pearl: OCA is an **FXR** agonist; **FXR** is a bile-acid sensor regulating synthesis and transport.

Question 42. PBC; fibrates; PPAR-alpha

A fibrate is added to a patient with cholestatic **PBC** biochemistry.

Lead-in: Which nuclear receptor effect is most relevant?

A. **PDC-E2** blockade depletes **AMA**
B. **PPAR-alpha** activation alters bile acid/phospholipid handling, including **MDR3**-related phospholipid transport
C. **V2 receptor** antagonism increases aquaresis
D. **NS5A** inhibition blocks viral assembly
E. **CD81** blockade prevents B-cell activation
Answer: B | Mechanism pearl: Fibrates are **PPAR-alpha** agonists with anticholestatic and metabolic effects.

Question 43. cholestyramine; pruritus

A cholestatic patient with pruritus is given **cholestyramine** separated from other medications.

Lead-in: Which mechanism explains the separation requirement?

A. **NTCP** inhibition traps drugs inside hepatocytes
B. **V1 receptor** activation reduces intestinal blood flow
C. **GABA-A** blockade prevents drug absorption
D. Luminal bile acid resin binding can also bind co-administered drugs and reduce absorption
E. CYP3A4 induction causes all drugs to become inactive immediately
Answer: D | Mechanism pearl: Cholestyramine is a nonspecific luminal binder; timing matters.

Question 44. pruritus; rifampicin; PXR

Rifampicin improves cholestatic pruritus in a patient intolerant to **cholestyramine**.

Lead-in: Which molecular mechanism best explains its anticholestatic-pruritus role?

A. **PXR** activation induces detoxification and transporter pathways for pruritogenic compounds
B. **BSEP** loss causing bile-acid retention
C. **IL-17** neutralization
D. Selective V2 antagonism
E. Direct mu-opioid receptor antagonism
Answer: A | Mechanism pearl: Rifampicin is a **PXR** ligand and enzyme inducer; hepatotoxicity monitoring is required.

Question 45. cholestatic pruritus; naltrexone

A patient with severe cholestatic pruritus improves with **naltrexone** but develops transient withdrawal-like symptoms.

Lead-in: Which mechanism is most consistent?

A. **FXR** agonism suppresses **CYP7A1**
B. **PXR** induction of **MRP2**

C. Histamine H1 blockade in dermal mast cells
D. Opioid receptor antagonism counteracts increased endogenous opioidergic tone in cholestasis
E. Bile acid binding in the intestinal lumen
Answer: D | Mechanism pearl: Cholestatic itch is not simply histamine; opioid pathways can be clinically relevant.

Question 46. PFIC2; BSEP

An infant has low-GGT cholestasis from ABCB11 mutation.

Lead-in: Which transporter is defective?

A. **NTCP**, the basolateral sodium-taurocholate cotransporter
B. **MRP2**, the conjugated bilirubin transporter
C. **OATP**1B1/1B3, hepatic organic anion uptake transporters
D. **BSEP**, the canalicular bile salt export pump
E. **MDR3**, the phosphatidylcholine floppase
Answer: D | Mechanism pearl: PFIC2 is **BSEP** deficiency and causes low-GGT hepatocellular cholestasis.

Question 47. PFIC3; MDR3; GGT

A child has cholestasis with high GGT and **MDR3** deficiency.

Lead-in: What mechanism explains high-GGT injury?

A. Failure of bile salt export keeps bile non-detergent and low-GGT
B. Reduced biliary phospholipid secretion leaves bile salts unbuffered, injuring cholangiocytes and biliary epithelium
C. Defective copper excretion causes Kayser-Fleischer rings
D. B-cell **CD81** stimulation causes **MPGN**
E. Impaired bilirubin conjugation causes isolated unconjugated jaundice
Answer: B | Mechanism pearl: **MDR3** deficiency reduces protective phosphatidylcholine in bile; detergent bile injures ducts and raises GGT.

Question 48. ICP; bile acids; transporters

A pregnant woman develops intense pruritus, high bile acids, and mild aminotransferase elevation in the third trimester.

Lead-in: Which mechanism is most plausible?

A. Irreversible **PDC-E2** destruction by **AMA**
B. Acute loss of **ATP7B** causing copper hemolysis
C. Anti-**HCV immune complex**es depositing in bile ducts
D. Type I interferon-induced **cccDNA** clearance
E. Hormonal inhibition of canalicular bile acid transport in genetically susceptible hepatobiliary transport pathways
Answer: E | Mechanism pearl: ICP reflects pregnancy-triggered transporter dysfunction; fetal risk correlates with bile acids.

Question 49. PSC; IBD; cholangiopathy

A man with ulcerative colitis has multif**oca**l biliary strictures and cholestatic tests. Steroids do not normalize the cholangiogram.

Lead-in: Which mechanism best fits **PSC**?

A. **AMA**-mediated destruction of only small intrahepatic ducts
B. **IgG4** plasma-cell disease that always resolves with steroids
C. Pure bile salt export pump deficiency
D. Chronic immune-mediated cholangiopathy linked to gut-liver immune t**raf**ficking and microbiome signals
E. **HCV** B-cell cryoglobulin deposition in large ducts
Answer: D | Mechanism pearl: **PSC** is not simply a steroid-responsive autoimmune hepatitis; it is a fibro-obliterative cholangiopathy strongly linked to IBD.

Question 50. IgG4 cholangitis

A patient with biliary strictures, pancreatic enlargement, high **IgG4**, and steroid responsiveness is suspected of **IgG4**-related cholangitis.

Lead-in: Which mechanism distinguishes it from classic **PSC**?

A. ABCB11 bile salt export pump loss
B. **PDC-E2**-specific autoimmune ductopenia only
C. **HBV cccDNA** persistence in cholangiocytes
D. **HCV CD81**-driven B-cell **cryoglobulinemia**
E. **IgG4**-related lymphoplasmacytic fibroinflammation with steroid-responsive organ involvement
Answer: E | Mechanism pearl: **IgG4**-related disease can mimic **PSC** or **cholangiocarcinoma** but has different systemic biology and steroid responsiveness.

Question 51. PSC; CA19-9; CCA

A PSC patient develops a dominant stricture and rising CA19-9 during cholangitis.

Lead-in: Which interpretation is most precise?

A. CA19-9 is suppressed by bacterial cholangitis
B. CA19-9 is a direct measure of BSEP activity
C. CA19-9 is perfectly specific for cholangiocarcinoma in PSC
D. CA19-9 reflects AFP-L3 glycosylation in HCC
E. CA19-9 is a supportive biomarker but can rise from obstruction/inflammation and cannot alone diagnose cholangiocarcinoma
Answer: E | Mechanism pearl: Tumor biomarkers must be interpreted with biliary obstruction, infection, and imaging/cytology context.

Question 52. HCC; arterialization

A patient with cirrhosis has a liver nodule showing arterial phase hyperenhancement and washout.

Lead-in: Which pathobiology explains this imaging pattern?

A. Hepatocarcinogenesis progressively shifts blood supply toward unpaired arterial neovascularization
B. Bile acids produce delayed venous enhancement
C. HCC is supplied only by portal venous branches
D. Regenerating nodules lose all arterial supply
E. DCP directly causes contrast washout
Answer: A | Mechanism pearl: HCC imaging reflects arterialization and reduced portal supply during malignant transformation.

Question 53. HCC; AFP

AFP is normal in a patient with imaging-diagnosed HCC.

Lead-in: What biomarker principle does this illustrate?

A. AFP only rises in cholangiocarcinoma
B. AFP is never produced by HCC
C. AFP is a marker of bile acid transporter failure
D. Normal AFP excludes vascular invasion
E. AFP lacks sufficient sensitivity and specificity to exclude or confirm HCC by itself
Answer: E | Mechanism pearl: HCC diagnosis cannot rely on AFP alone; imaging context and other biomarkers may assist.

Question 54. AFP-L3; HCC biomarker

A patient with a small HCC has high AFP-L3 fraction despite modest total AFP.

Lead-in: What does AFP-L3 represent?

A. A cryoglobulin fraction containing IgM RF
B. A fucosylated AFP glycoform associated with malignant hepatocyte biology
C. A des-carboxylated coagulation factor caused by vitamin K absence only
D. An unconjugated bilirubin isoform from UGT1A1 deficiency
E. A bile-acid transporter fragment from BSEP
Answer: B | Mechanism pearl: AFP-L3 adds glycoform biology to total AFP interpretation.

Question 55. DCP; HCC biomarker

A patient with HCC has high des-gamma-carboxy prothrombin.

Lead-in: Which mechanism explains this biomarker?

A. Low C4 from classical complement activation
B. PXR activation of CYP enzymes
C. TSPO-induced neurosteroid synthesis
D. Abnormal prothrombin carboxylation by malignant hepatocytes generates DCP/PIVKA-II
E. Hepcidin deficiency causing ferroportin excess
Answer: D | Mechanism pearl: DCP reflects abnormal vitamin K-dependent prothrombin processing in HCC, not simply coagulation failure.

Question 56. sorafenib; RAF; VEGFR

A patient with advanced HCC is treated with sorafenib.

Lead-in: Which signaling targets explain its antitumor effect?

A. Selective NS5B RNA polymerase inhibition
B. Multikinase inhibition including RAF pathway and VEGFR/PDGFR-mediated angiogenesis signaling
C. GABA-A receptor antagonism
D. PDC-E2 depletion from biliary epithelium

E. **V1 receptor** agonism with renal vasoconstriction reversal
Answer: B | Mechanism pearl: **Sorafenib** targets proliferative and angiogenic signaling rather than a single liver-specific antigen.

Question 57. checkpoint inhibitor; hepatitis

A patient develops autoimmune-like hepatitis after immune checkpoint inhibitor therapy.

Lead-in: Which mechanism is most likely?

A. **V2 receptor** activation causing hepatocyte edema
B. Direct **CYP2E1** **NAPQI** formation in every patient
C. IgM RF **immune complex**es caused by **HCV** **CD81** binding
D. **BSEP** mutation causing inherited cholestasis
E. Disinhibition of antitumor T-cell pathways can break hepatic immune tolerance and cause T-cell-mediated hepatitis
Answer: E | Mechanism pearl: Checkpoint inhibitors can unmask immune-mediated liver injury; biopsy may resemble autoimmune hepatitis but context matters.

Question 58. MASLD; insulin resistance

A man with **MASH** has **insulin resistance** and increasing hepatic fat.

Lead-in: Which metabolic flux is central?

A. **PDC-E2** immune destruction of bile ducts
B. **Insulin resistance** increases adipose lipolysis and hepatic free fatty acid delivery, promoting triglyceride accumulation
C. V1-mediated splanchnic vasoconstriction
D. Complete absence of dietary fat absorption
E. **HBV cccDNA**-driven triglyceride synthesis
Answer: B | Mechanism pearl: **MASLD** begins with metabolic substrate oversupply and **insulin resistance**; injury requires additional lipotoxic stress.

Question 59. MASH; stellate cells; fibrosis

A **MASH** biopsy shows ballooning, lobular inflammation, and pericellular fibrosis.

Lead-in: Which mechanism links lipotoxic injury to fibrosis?

A. **NS5A** inhibition causes matrix remodeling
B. **V2 receptor** signaling activates portal fibroblasts exclusively
C. IgM RF complexes deposit in space of Disse
D. Direct bilirubin conjugation failure causes collagen deposition
E. Hepatocyte stress activates Kupffer-cell cytokines and hepatic **stellate cells**, increasing matrix deposition
Answer: E | Mechanism pearl: Fibrosis is a wound-healing response driven by injured hepatocytes, inflammatory **macrophage**s, and activated **stellate cells**.

Question 60. MASH; pioglitazone; PPAR-gamma

A trial of pioglitazone improves steatohepatitis in selected patients.

Lead-in: Which receptor mechanism best explains benefit?

A. V1 agonism raises portal pressure
B. **FXR** antagonism increases bile acid synthesis
C. **BSEP** inhibition reduces hepatocyte triglyceride
D. PPAR-gamma activation improves insulin sensitivity and adipose-liver metabolic flux
E. **GABA-A** blockade improves ballooning
Answer: D | Mechanism pearl: PPAR-gamma agonism addresses metabolic **insulin resistance**, a driver of **MASH**.

Question 61. MASH; vitamin E

Vitamin E is considered for a non-diabetic patient with biopsy-proven **MASH**.

Lead-in: Which mechanistic rationale is most relevant?

A. **V2 receptor** antagonism
B. Copper chelation from hepatocyte lysosomes
C. Direct insulin receptor agonism
D. Antioxidant reduction of **oxidative stress**-mediated hepatocellular injury
E. **HBV** reverse transcriptase inhibition
Answer: D | Mechanism pearl: Vitamin E targets oxidative injury, not the upstream drivers of **insulin resistance**.

Question 62. alcoholic hepatitis; LPS; Kupffer

A patient with alcohol-associated hepatitis has fever, jaundice, **neutrophil**ia, and high bilirubin.

Lead-in: Which inflammatory pathway is central?

A. Gut-derived **LPS** activates **Kupffer cells** and cytokine networks including **TNF-alpha**, recruiting **neutrophil**s
B. **HCV** **CD81** binding causes IgM RF deposition
C. **BSEP** deficiency causes low-GGT cholestasis
D. **PDC-E2**-specific **AMA** destroys interlobular ducts
E. **FGFR4** activation suppresses **CYP7A1**
Answer: A | Mechanism pearl: Alcoholic hepatitis is an inflammatory syndrome driven by gut-liver axis, innate immunity, and hepatocyte injury.

Question 63. alcoholic hepatitis; Lille

A severe alcoholic hepatitis patient is reassessed after 7 days of **corticosteroids** with a **Lille** score.

Lead-in: What does **Lille** score biologically approximate?

A. Early bilirubin response as a surrogate for steroid-responsive inflammatory injury
B. Genetic risk of **HFE** **hepcidin** deficiency
C. Amount of **manganese** deposition in basal ganglia
D. Severity of portal-vein thrombosis
E. Degree of **cccDNA** persistence in hepatocytes
Answer: A | Mechanism pearl: **Lille** separates steroid responders from nonresponders and prevents futile immunosuppression.

Question 64. fibrosis; TGF-beta; stellate cells

A fibrogenesis drug blocks **TGF-beta** signaling in activated hepatic **stellate cells**.

Lead-in: Which biologic process is directly targeted?

A. Bile acid binding in the intestinal lumen
B. **HCV** **NS5B** polymerase activity
C. **GABA-A** chloride-channel opening
D. Transdifferentiation to collagen-producing myofibroblast-like cells and extracellular matrix deposition
E. Hepatocyte **cccDNA** formation
Answer: D | Mechanism pearl: **TGF-beta** is a key profibrogenic signal for stellate-cell matrix production.

Question 65. fibrosis; PDGF

Another antifibrotic strategy blocks **PDGF** receptor signaling.

Lead-in: Which stellate-cell behavior is most affected?

A. Bile acid binding to **FXR**
B. Proliferation and migration of activated **stellate cells**
C. Copper incorporation into ceruloplasmin
D. IgM RF binding to IgG
E. **Ammonia** conversion to **glutamine**
Answer: B | Mechanism pearl: **PDGF** is a potent mitogenic and chemotactic signal for activated **stellate cells**.

Question 66. sinusoidal capillarization

A cirrhotic liver biopsy shows sinusoidal capillarization.

Lead-in: Which functional consequence is most important?

A. Direct elimination of stellate-cell activation
B. Loss of fenestration and matrix deposition impair exchange between sinusoidal blood and hepatocytes
C. Complete restoration of normal portal venous flow
D. Improved hepatocyte oxygenation through wider fenestrae
E. Selective destruction of **Kupffer cells** only
Answer: B | Mechanism pearl: Capillarization converts the sinusoid toward a less permeable capillary-like structure and worsens resistance/exchange.

Question 67. hemochromatosis; hepcidin; ferroportin

A patient has hereditary hemochromatosis from **HFE** mutation.

Lead-in: Which iron-regulatory defect is central?

A. **MRP2** failure prevents conjugated bilirubin export
B. **BSEP** failure causes low-GGT cholestasis
C. Inappropriately low **hepcidin** allows excessive **ferroportin**-mediated intestinal iron export into plasma
D. High **hepcidin** traps iron in enterocytes and **macrophage**s
E. **ATP7B** failure prevents biliary copper excretion
Answer: C | Mechanism pearl: Most **HFE** hemochromatosis is **hepcidin** deficiency relative to iron load, causing increased absorption.

Question 68. HFE; iron distribution

A patient has high ferritin, high transferrin saturation, and iron in hepatocytes.

Lead-in: Which cell distribution favors classic **HFE** hemochromatosis?

A. IgG plasma-cell portal infiltrates only
B. Predominant Kupffer-cell iron trapping from **ferroportin** loss
C. Parenchymal hepatocyte iron loading from increased plasma iron delivery
D. Pure biliary epithelial copper accumulation
E. Canalicular bile plug without iron

Answer: C | Mechanism pearl: HFE disease loads hepatocytes; **ferroportin** disease more often traps iron in **macrophage**s with different transferrin saturation patterns.

Question 69. ferroportin disease

A family has autosomal dominant hyperferritinemia with **macrophage** iron retention and normal/low transferrin saturation.

Lead-in: Which mechanism best fits **ferroportin** disease?

A. HFE loss causes **hepcidin** overproduction
B. ATP7B loss impairs biliary copper excretion
C. UGT1A1 promoter variants reduce bilirubin conjugation
D. Loss-of-function **ferroportin** impairs iron export from **macrophage**s
E. FXR activation suppresses **CYP7A1**

Answer: D | Mechanism pearl: Ferroportin disease differs from classic **HFE** hemochromatosis by **macrophage** iron trapping and often lower transferrin saturation.

Question 70. Wilson; ATP7B

A young woman with **Wilson** disease has low ceruloplasmin and neurologic signs.

Lead-in: Which molecular defect explains the disease?

A. PDC-E2 immunity destroys bile ducts
B. MRP2 loss blocks conjugated bilirubin secretion
C. ATP7B dysfunction impairs copper incorporation into ceruloplasmin and biliary copper excretion
D. HFE loss lowers **hepcidin** and increases iron absorption
E. BSEP loss blocks bile salt export

Answer: C | Mechanism pearl: Wilson disease is a copper-transport disorder centered on **ATP7B** in hepatocytes.

Question 71. Wilson ALF; copper hemolysis

A **Wilson** patient with acute liver failure has Coombs-negative hemolysis.

Lead-in: Which mechanism is most likely?

A. V2 receptor excess causes osmotic hemolysis
B. IgM RF **immune complex**es lyse red cells through **C4**
C. Massive hepatocellular copper release causes oxidative red-cell injury
D. Hepcidin deficiency ruptures erythrocytes
E. BSEP deficiency causes direct splenic sequestration

Answer: C | Mechanism pearl: Wilson ALF classically combines liver failure and Coombs-negative hemolysis due to copper toxicity.

Question 72. Wilson; zinc; metallothionein

Zinc is used as maintenance therapy in **Wilson** disease.

Lead-in: Which mechanism explains its effect?

A. Direct chelation of serum copper with urinary excretion as the main effect
B. Inhibition of **hepcidin** to increase **ferroportin**
C. Blockade of **BSEP** to reduce bile flow
D. Induction of intestinal **metallothionein** traps dietary copper in enterocytes, reducing absorption
E. Activation of **ATP7B** to increase biliary excretion

Answer: D | Mechanism pearl: Zinc reduces copper entry; chelators mobilize copper for excretion.

Question 73. D-penicillamine; proteinuria

A **Wilson** patient develops proteinuria after **D-penicillamine**.

Lead-in: Which mechanism is most consistent?

A. HFE suppression causing renal iron overload
B. HBV cccDNA activation in podocytes
C. BSEP induction causing renal bile acid deposition

D. Expected marker of effective copper chelation that should be ignored
E. Drug-induced immune-mediated renal injury related to chelator therapy
Answer: E | Mechanism pearl: Penicillamine can cause proteinuria/nephrotoxicity and autoimmune complications; monitoring is essential.

Question 74. A1AT; ER retention

A patient with **A1AT** deficiency has PAS-positive diastase-resistant globules in hepatocytes.

Lead-in: Which pathogenesis is correct?

A. IgM RF complexes form cytoplasmic globules
B. Loss of circulating antiprotease activity directly digests hepatocytes
C. Copper retention in lysosomes causes globules
D. BSEP failure forms PAS-positive bile salts
E. Misfolded mutant **A1AT** polymers accumulate in endoplasmic reticulum causing proteotoxic liver injury
Answer: E | Mechanism pearl: Lung disease is loss of function; liver disease is toxic gain-of-function from retained polymers.

Question 75. Gilbert; UGT1A1

A fasting adolescent has intermittent unconjugated hyperbilirubinemia with normal enzymes.

Lead-in: Which mechanism best explains Gilbert syndrome?

A. MRP2 canalicular export failure
B. ATP7B copper transport failure
C. Reduced **UGT1A1**-mediated bilirubin conjugation capacity
D. OATP1B1/1B3 uptake failure
E. Hepcidin deficiency
Answer: C | Mechanism pearl: Gilbert syndrome is benign reduced conjugation, often unmasked by fasting or illness.

Question 76. Dubin-Johnson; MRP2

A patient has chronic conjugated hyperbilirubinemia and darkly pigmented liver.

Lead-in: Which transporter defect is most likely?

A. Ferroportin gain-of-function
B. UGT1A1 promoter reduction
C. OATP1B1/1B3 dual loss
D. BSEP overactivity
E. MRP2/cMOAT impairment of canalicular conjugated bilirubin excretion
Answer: E | Mechanism pearl: Dubin-Johnson syndrome is impaired canalicular excretion of conjugated organic anions.

Question 77. Rotor; OATP

A patient has conjugated hyperbilirubinemia without dark liver pigment, due to impaired hepatic reuptake of conjugated bilirubin.

Lead-in: Which mechanism best fits Rotor syndrome?

A. ATP8B1 aminophospholipid transport failure
B. Defective **OATP**1B1/**OATP**1B3-mediated sinusoidal organic anion uptake
C. HFE hepcidin deficiency
D. MRP2 canalicular transport failure with pigment deposition
E. UGT1A1 conjugation failure
Answer: B | Mechanism pearl: Rotor syndrome reflects hepatic storage/reuptake defects and lacks the black liver of Dubin-Johnson.

Question 78. HPS; intrapulmonary dilatation

A patient with hypoxemia from cirrhosis has delayed bubbles in the left heart after contrast echocardiography.

Lead-in: Which mechanism best explains hepatopulmonary syndrome?

A. Alveolar destruction from **A1AT** polymers
B. Pulmonary arterial vasoconstriction with high vascular resistance
C. Acute thrombotic occlusion of pulmonary arteries
D. Left-to-right intracardiac shunt only
E. Intrapulmonary vascular dilatation and diffusion-perfusion mismatch driven by vasodilatory mediators
Answer: E | Mechanism pearl: HPS is cirrhosis plus abnormal oxygenation plus intrapulmonary vascular dilatation.

Question 79. POPH; pulmonary vascular resistance

Another cirrhotic patient has dyspnea, high mean pulmonary artery pressure, and elevated pulmonary vascular resistance.

Lead-in: Which mechanism best fits portopulmonary hypertension?

A. Portal vein thrombosis causing pulmonary embolism in all cases
B. Pulmonary vascular remodeling and vasoconstriction causing increased pulmonary vascular resistance
C. **Astrocyte glutamine** accumulation
D. Intrapulmonary vascular dilatation causing low resistance
E. Dilutional hyponatremia from **AVP** excess
Answer: B | Mechanism pearl: POPH is pulmonary arterial hypertension in **portal hypertension**; it is physiologically opposite to **HPS**.

Question 80. Budd-Chiari

A woman with abdominal pain, hepatomegaly, ascites, and hepatic vein thrombosis is diagnosed with **Budd-Chiari** syndrome.

Lead-in: Which primary hemodynamic lesion explains the syndrome?

A. Hepatocyte bile salt export failure
B. Direct bilirubin conjugation failure
C. Hepatic venous outflow obstruction causing sinusoidal congestion and **portal hypertension**
D. Bile duct epithelial autoimmune destruction
E. Portal venous inflow overproduction from splanchnic NO
Answer: C | Mechanism pearl: Budd-Chiari is post-sinusoidal outflow obstruction; search for myeloproliferative and thrombophilic drivers.

Question 81. sinusoidal obstruction syndrome

A bone marrow transplant recipient develops painful hepatomegaly, jaundice, weight gain, and ascites after conditioning therapy.

Lead-in: Which mechanism best explains **sinusoidal obstruction syndrome**?

A. **HCV CD81** B-cell activation
B. Autoimmune bile duct destruction by **AMA**
C. **IgG4** plasma-cell infiltration of the pancreas
D. **BSEP** genetic absence from birth
E. Toxic sinusoidal endothelial injury causes sinusoidal narrowing, congestion, and postsinusoidal **portal hypertension**
Answer: E | Mechanism pearl: SOS is primarily endothelial/sinusoidal injury, not classic large hepatic vein thrombosis.

Question 82. ischemic hepatitis; zone 3

A patient in shock develops AST/ALT in the thousands with modest bilirubin rise.

Lead-in: Which lobular zone is most vulnerable and why?

A. Zone 1 periportal hepatocytes because bile acids enter there first
B. **Zone 3** centrilobular hepatocytes because they have lowest oxygen tension and high CYP activity
C. Bile ducts because they lack arterial blood supply
D. Portal tracts because **Kupffer cells** are absent there
E. Caudate lobe only because it drains separately
Answer: B | Mechanism pearl: Ischemic and many toxic injuries accentuate in **zone 3** due to oxygen gradient and metabolic enzyme distribution.

Question 83. congestive hepatopathy

A patient with right heart failure has cholestatic enzymes and tender hepatomegaly.

Lead-in: Which mechanism explains congestive hepatopathy?

A. **HBV cccDNA** expansion from venous congestion
B. Urea-cycle hyperactivation
C. **AMA**-mediated ductopenia
D. Elevated central venous pressure transmits to hepatic sinusoids causing **zone 3** congestion and hypoxic injury
E. Reduced **BSEP** expression from inherited mutation only
Answer: D | Mechanism pearl: Congestive hepatopathy is hemodynamic liver disease from venous pressure and sinusoidal congestion.

Question 84. rebalanced hemostasis

A cirrhotic patient has prolonged INR but no active bleeding. A junior says he is auto-anticoagulated.

Lead-in: Which concept is correct?

A. Vitamin K always corrects cirrhotic coagulopathy
B. Platelet count alone predicts bleeding risk precisely
C. Cirrhosis produces **rebalanced hemostasis** with parallel reductions in procoagulant and anticoagulant factors
D. Elevated INR proves absence of thrombin generation
E. Cirrhosis protects completely against venous thrombosis
Answer: C | Mechanism pearl: INR is not a global bleeding-risk test in cirrhosis; thrombosis and bleeding can both occur.

Question 85. portal vein thrombosis; rebalanced hemostasis

A cirrhotic patient develops portal vein thrombosis despite INR 2.0.

Lead-in: Which mechanism best explains why thrombosis can occur?

A. INR directly measures portal flow velocity
B. Low fibrinogen prevents all thrombosis
C. **Thrombopoietin** excess always causes thrombocytosis
D. Reduced anticoagulant proteins, endothelial activation, sluggish portal flow, and inflammation overcome INR-based assumptions
E. Bilirubin directly dissolves portal thrombi

Answer: D | Mechanism pearl: Cirrhotic PVT reflects rebalanced but fragile hemostasis plus l**ocal** flow and endothelial factors.

Question 86. thrombocytopenia; thrombopoietin

A man with advanced cirrhosis has thrombocytopenia out of proportion to bleeding symptoms.

Lead-in: Which mechanism contributes beyond splenic sequestration?

A. **UGT1A1** deficiency causes immune thrombocytopenia
B. Reduced hepatic **thrombopoietin** production limits marrow platelet generation
C. **BSEP** loss prevents megakaryocyte maturation
D. High **hepcidin** directly destroys platelets
E. **TSPO** activation traps platelets in brain

Answer: B | Mechanism pearl: Platelet count in cirrhosis reflects hypersplenism and reduced **thrombopoietin** among other factors.

Question 87. ACLF; systemic inflammation

In acute-on-chronic liver failure, a patient develops renal, cerebral, and circulatory failure after infection.

Lead-in: Which mechanism is most central?

A. Systemic inflammation triggers immune-metabolic decompensation and multiorgan failure on a cirrhotic background
B. Selective **albumin** deficiency without inflammation
C. Pure portal pressure increase without immune activation
D. Congenital **BSEP** loss presenting in adulthood
E. Isolated bilirubin conjugation failure explains all organ failures

Answer: A | Mechanism pearl: ACLF is not just high MELD; it is acute decompensation with intense inflammation and extrahepatic organ failures.

Question 88. SBP; albumin; renal dysfunction

A patient with SBP receives **albumin** with antibiotics to prevent kidney injury.

Lead-in: Which non-antibiotic mechanism is most relevant?

A. **Albumin** activates **HBV** polymerase inhibition
B. **Albumin** chelates copper like **trientine**
C. **Albumin** antagonizes **GABA-A** receptors
D. **Albumin** directly kills gram-negative bacteria
E. Plasma expansion and binding/modulation of inflammatory mediators stabilize effective arterial volume and circulatory function

Answer: E | Mechanism pearl: Albumin in SBP is more than oncotic support; it modifies circulatory dysfunction and inflammation risk.

Question 89. FGF19; FGFR4; CYP7A1

A trial drug mimics FGF19 signaling in cholestasis.

Lead-in: Which pathway is intended?

A. **GABA-A** activation reduces neuroinflammation
B. **FGFR4**-mediated ERK signaling suppresses **CYP7A1** and reduces bile acid synthesis
C. **CD81** blockade prevents cryoglobulin formation
D. **MRP2** inhibition increases bilirubin retention
E. **V2 receptor** blockade increases aquaresis

Answer: B | Mechanism pearl: The **FXR**-FGF19-**FGFR4** axis is negative feedback on bile acid synthesis.

Question 90. FXR; bile acids

A bile-acid sensor is activated in cholestasis and changes transporter expression.

Lead-in: Which nuclear receptor is most directly acting as the bile acid sensor?

A. **GABA-A** receptor
B. **CD81** receptor
C. **FXR**
D. **V1 receptor**

E. PD-1 receptor
Answer: C | Mechanism pearl: FXR regulates bile acid synthesis and transport, linking bile acid levels to transcriptional adaptation.

Question 91. cholestasis; NTCP; MRP3/4

A patient with cholestasis has adaptive downregulation of **NTCP** and upregulation of basolateral efflux transporters.

Lead-in: What is the purpose of this response?

A. Increase **ammonia** detoxification by **astrocyte**s
B. Increase canalicular bile acid concentration at all costs
C. Trap bile acids permanently inside mitochondria
D. Activate IgM RF **immune complex**es
E. Limit hepatocyte bile-acid uptake and promote back-export into blood when canalicular excretion is impaired
Answer: E | Mechanism pearl: Cholestatic adaptation protects hepatocytes by reducing intracellular bile acid toxicity.

Question 92. Dubin-Johnson; MRP2

A patient with Dubin-Johnson syndrome has conjugated hyperbilirubinemia but otherwise benign course.

Lead-in: Which principle explains the relative benignity?

A. It is caused by complete absence of bile acids
B. It produces no bilirubin conjugation at all
C. It is identical to **Wilson** disease
D. It rapidly progresses to cirrhosis in all adults
E. Defect is mainly canalicular organic anion export, not global hepatocellular synthetic failure
Answer: E | Mechanism pearl: Transporter defects can produce impressive bilirubin abnormalities without severe hepatocyte failure.

Question 93. PBC; transplant indications

A patient with **PBC** has fatigue but no decompensation and asks if fatigue alone indicates liver transplantation.

Lead-in: Which reasoning is best?

A. Fatigue alone always equals occult HCC
B. Fatigue is important but poorly correlated with liver failure severity and is not by itself a transplant indication
C. Fatigue proves steroid-responsive **IgG4** cholangitis
D. Fatigue is caused by high **AFP-L3** and requires resection
E. Fatigue reflects direct **V1 receptor** toxicity
Answer: B | Mechanism pearl: PBC symptom burden and liver-failure risk are not identical; transplant decisions require objective disease severity or intractable complications.

Question 94. HBV; HCC risk

A patient with chronic **HBV** and normal ALT asks why HCC surveillance may still be needed.

Lead-in: Which mechanism supports persistent risk?

A. HBV cannot cause HCC without **HCV** coinfection
B. HBV risk disappears immediately when ALT normalizes
C. HBV can promote **car**cinogenesis through integration, chronic immune injury, and oncogenic effects even before cirrhosis in high-risk groups
D. HBV only causes **cholangiocarcinoma** through **CA19-9**
E. HBsAg prevents malignant transformation
Answer: C | Mechanism pearl: HBV differs from many liver diseases because HCC risk may exist without established cirrhosis.

Question 95. HCV SVR; HCC surveillance

A patient with **HCV** cirrhosis achieves SVR but remains in surveillance.

Lead-in: Which mechanism explains residual HCC risk?

A. SVR increases **cccDNA** persistence
B. HCV antibodies become oncogenic after cure
C. Eradication removes viral replication but does not fully reverse established cirrhotic field injury and genomic risk
D. DAAs directly induce HCC in all patients
E. SVR prevents fibrosis regression
Answer: C | Mechanism pearl: SVR reduces but does not abolish HCC risk once advanced fibrosis/cirrhosis exists.

Question 96. HCV; PCT

A patient with porphyria cutanea tarda and **HCV** improves after viral clearance and iron reduction.

Lead-in: Which mechanism best links **HCV**/iron to PCT?

A. Iron deficiency activates **PDC-E2** antibodies
B. **BSEP** overexpression traps porphyrins in bile
C. **AVP** excess inhibits heme synthesis in skin
D. **HCV** directly produces porphyrins through **NS5B**
E. Oxidative hepatic stress inhibits uroporphyrinogen decarboxylase activity, promoting porphyrin accumulation
Answer: E | Mechanism pearl: PCT is a hepatic porphyrin disorder promoted by iron, alcohol, estrogen, and **HCV**-related **oxidative stress**.

Question 97. cholestasis; lipoprotein X

A patient with severe cholestasis has xanthomas and hypercholesterolemia.

Lead-in: Which lipoprotein abnormality is classically involved?

A. Complete absence of HDL from ABCA1 deficiency
B. Excess chylomicron remnants from LPL deficiency only
C. Low LDL from **hepcidin** deficiency
D. **DCP** release from HCC
E. Cholestasis can generate abnormal lipoprotein X with impaired biliary cholesterol excretion
Answer: E | Mechanism pearl: Cholestatic hypercholesterolemia differs mechanistically from typical LDL-driven familial hypercholesterolemia.

Question 98. hepatocyte synthetic function

A patient with liver failure has low **albumin**, low clotting factors, and edema.

Lead-in: Which hepatocyte function is failing?

A. **Ammonia** detoxification by **astrocyte**s
B. B-cell immunoglobulin synthesis in hepatocytes
C. Intestinal **metallothionein** induction
D. Synthesis of major plasma proteins, except immunoglobulins
E. **FGFR4**-mediated bile acid feedback only
Answer: D | Mechanism pearl: Hepatocytes synthesize **albumin** and most clotting factors; immunoglobulins are made by plasma cells.

Question 99. Kupffer cell; innate immunity

A researcher studies liver **macrophage**s in alcohol-related injury.

Lead-in: Which cell is the resident **macrophage** central to portal endotoxin sensing?

A. Kupffer cell
B. Stellate cell
C. Cholangiocyte
D. Pit cell only
E. Hepatic progenitor cell
Answer: A | Mechanism pearl: **Kupffer cells** clear gut-derived products and release cytokines that shape liver inflammation.

Question 100. stellate cell; fibrosis

A translational antifibrotic therapy tries to keep hepatic **stellate cells** quiescent.

Lead-in: Which normal function would be preserved by quiescence?

A. **HBV** reverse transcription
B. **GABA-A** chloride conductance
C. IgM RF immune-complex deposition
D. Vitamin A/retinoid storage in the space of Disse rather than collagen-producing myofibroblast activation
E. Copper incorporation into ceruloplasmin
Answer: D | Mechanism pearl: Quiescent **stellate cells** store retinoids; activated **stellate cells** contract and produce extracellular matrix.

Section B - 50 Moderate-to-Long Case Scenario MCQs

Question 101. HRS; SBP; circulatory dysfunction

A 59-year-old man with alcohol-related cirrhosis is admitted with tense ascites and SBP. After 48 hours of cefotaxime and **albumin**, creatinine continues to rise. Urine sodium is very low; urinalysis has no significant protein or hematuria and renal ultrasound is normal. Blood pressure is 88/55 mmHg with warm extremities.

Lead-in: Which integrated mechanism best explains his renal failure?

A. **Portal hypertension** and systemic inflammation cause **splanchnic vasodilatation**, effective arterial underfilling, **RAAS/SNS/AVP** activation, and intense renal vasoconstriction
B. Immune-complex glomerulonephritis from **IgM rheumatoid factor** deposition
C. Drug-induced interstitial nephritis as the defining mechanism of HRS
D. Primary renal artery thrombosis from **rebalanced hemostasis**
E. Direct bilirubin crystallization obstructing renal tubules
Answer: A | Mechanism pearl: HRS is diagnosed after excluding structural renal disease. The renal vasoconstriction is secondary to circulatory dysfunction, not primary kidney inflammation.

Question 102. hyponatremia; AVP; cirrhosis

A 63-year-old cirrhotic patient with ascites develops Na 119 mmol/L. He is clinically hypervolemic, has low serum osmolality, and has inappropriately concentrated urine. His family asks why more total body water can coexist with low effective circulation.

Lead-in: Which mechanism provides the best explanation?

A. Splanchnic arterial vasodilatation lowers effective arterial volume, triggering non-osmotic **AVP** release and renal water retention
B. Aldosterone deficiency causes free-water retention without sodium retention
C. Bile salt export pump failure directly inserts aquaporins
D. Hyper**albumin**emia increases oncotic water movement into the vascular space
E. Primary hypothalamic failure suppresses thirst and **AVP** release
Answer: A | Mechanism pearl: Cirrhotic hyponatremia is a neurohormonal response to arterial underfilling despite expanded extracellular volume.

Question 103. carvedilol; portal hypertension

A 54-year-old man with large varices and ascites is started on **carvedilol**. At follow-up, his pulse is lower and portal pressure has fallen more than expected with propranolol, but he reports postural dizziness.

Lead-in: Which pharmacologic explanation best integrates benefit and adverse effect?

A. It activates **FXR** and suppresses bile acid synthesis
B. It is a V1 agonist that increases systemic arterial tone without beta effects
C. It is a selective **beta-1** blocker that increases splanchnic vasoconstriction through **beta-2** stimulation
D. **Carvedilol** combines nonselective beta blockade with **alpha-1** blockade, reducing portal inflow and intrahepatic/systemic vascular tone
E. It inhibits aldosterone receptors and causes natriuresis
Answer: D | Mechanism pearl: The same **alpha-1** effect that enhances portal-pressure reduction can worsen hypotension in decompensated patients.

Question 104. HE; GI bleed; sarcopenia

A 48-year-old woman with NASH cirrhosis has repeated HE admissions. She takes **lactulose** but is sarcopenic and constipated. After a high-protein GI bleed, she becomes confused. **Ammonia** is elevated; CT brain is normal.

Lead-in: Which explanation best connects the trigger to the brain lesion?

A. Constipation decreases **ammonia** production by reducing bacterial contact time
B. GI bleeding activates **FXR** and suppresses **NMDA** receptors
C. Protein nitrogen and blood in the gut increase **ammonia**, which bypasses hepatic detoxification and is converted to **glutamine** within **astrocyte**s causing osmotic dysfunction
D. Protein intake causes copper release from hepatocytes and hemolysis
E. Blood digestion releases bilirubin that directly opens neuronal chloride channels
Answer: C | Mechanism pearl: GI bleeding is an **ammonia** load. Sarcopenia reduces peripheral detoxification, increasing HE susceptibility.

Question 105. HE; TSPO; GABA-A

A patient with covert HE participates in a study measuring neurosteroid activity. The study finds increased **mitochondrial TSPO** expression in **astrocyte**s and exaggerated GABAergic signaling. He transiently improves after flumazenil.

Lead-in: What is the best mechanistic interpretation?

A. **TSPO** is a bile acid receptor that increases **BSEP** expression in neurons

B. Flumazenil improves HE by inducing urea-cycle enzymes in hepatocytes
C. **Ammonia**/**manganese**-associated **TSPO** upregulation increases neurosteroid-mediated positive allosteric modulation of **GABA-A** receptors
D. **Manganese** deposition proves **Wilson** disease rather than HE
E. **GABA-A** activation is excitatory because it opens sodium channels
Answer: C | Mechanism pearl: This is the examiner-style trap: HE is not only **ammonia**; altered inhibitory neurotransmission can be tested.

Question 106. HCV; cryoglobulinemia; MPGN

A 56-year-old man with untreated chronic **HCV** presents with fatigue, arthralgia, palpable purpura, neuropathy, hypertension, proteinuria, hematuria, low **C4**, positive RF, positive cryoglobulins, and **MPGN**.

Lead-in: Which mechanism is responsible?

A. Chronic **HCV** antigenic stimulation expands B-cell clones producing **IgM rheumatoid factor** that binds anti-**HCV** IgG to form cryoprecipitable **immune complex**es
B. CD8 T-cell molecular mimicry against endothelial antigens
C. Plasma-cell monoclonal IgG hyperviscosity as isolated type I **cryoglobulinemia**
D. Direct cytopathic infection of vascular endothelium by **HCV**
E. Complement C3 genetic deficiency causing uncontrolled alternative pathway activation
Answer: A | Mechanism pearl: **HCV** mixed **cryoglobulinemia** is immune-complex vasculitis: IgM RF + IgG anti-**HCV** + low **C4** + **MPGN**.

Question 107. HBV reactivation; rituximab

A 61-year-old woman with chronic **HBV** and prior rituximab exposure develops jaundice and **HBV** DNA 10^8 IU/mL. She had anti-HBc positivity and low anti-HBs before chemotherapy.

Lead-in: Which mechanism best explains severe reactivation?

A. Rituximab directly converts **HCV** RNA into **HBV** DNA
B. **HBV** disappears after anti-HBs formation so this must be new infection
C. **HBV** reactivation requires **HDV** superinfection in all cases
D. Anti-HBc antibody acts as a viral polymerase and restarts replication
E. B-cell depletion and immunosuppression remove immune control over persistent **cccDNA**, allowing rapid **HBV** replication
Answer: E | Mechanism pearl: The reservoir is persistent **HBV** template; immune control, not complete viral eradication, maintains quiescence.

Question 108. DAA; HBV reactivation

A man with chronic **HCV** and occult **HBV** begins **DAA** therapy. Four weeks later **HCV** RNA is undetectable but ALT rises sharply and **HBV** DNA increases.

Lead-in: Which mechanism best explains the paradox?

A. **HCV** clearance blocks **NTCP** and traps **HBV** in blood
B. **DAA**s activate **FXR** and cause bile-acid-mediated hepatitis only
C. Rapid **HCV** suppression removes viral interference and permits **HBV** replication from persistent nuclear templates
D. **NS5A** inhibitors directly stimulate **HBV** polymerase
E. **HBV** reactivation occurs because **DAA**s destroy all **B cell**s
Answer: C | Mechanism pearl: Before **DAA** treatment, **HBV** markers matter. ALT flare after **HCV** suppression should trigger **HBV** DNA evaluation.

Question 109. AIH; Treg; Th17

A young woman has acute severe hepatitis with ANA/SMA positivity, IgG elevation, interface hepatitis, and many plasma cells. Viral markers are negative. She improves on prednisolone and **azathioprine**.

Lead-in: Which immunologic explanation is most complete?

A. **PDC-E2**-specific cholangiocyte destruction with isolated ductopenia
B. Copper accumulation from **ATP7B** failure
C. IgM RF immune-complex deposition in glomeruli and vessels
D. **BSEP** loss causing hepatocellular bile salt retention
E. Genetically influenced loss of tolerance permits CD4 helper, **Th17**, cytotoxic T-cell, and plasma-cell responses against hepatocyte antigens, insufficiently restrained by **Treg**s
Answer: E | Mechanism pearl: **AIH** questions may use autoantibodies as clues, but the mechanism is T-cell/plasma-cell immune dysregulation.

Question 110. AIH; azathioprine; TPMT

A 35-year-old woman with AIH achieves remission on steroids but relapses whenever prednisone is tapered. Azathioprine is planned. TPMT activity is low.

Lead-in: Which mechanism explains both efficacy and toxicity concern?

A. Azathioprine blocks IL-4R alpha and causes eosinophilia
B. Thiopurine metabolites suppress lymphocyte proliferation by interfering with purine synthesis, but impaired metabolism increases myelotoxic metabolite exposure
C. Azathioprine chelates copper and causes proteinuria
D. Azathioprine activates V2 receptors and causes hyponatremia
E. Azathioprine inhibits NS5B and selects HCV resistance
Answer: B | Mechanism pearl: Thiopurines are useful steroid-sparing drugs, but pharmacogenetic metabolism modifies safety.

Question 111. PBC; OCA; FXR

A 50-year-old woman with PBC has persistent ALP elevation after 1 year of UDCA. OCA is added. She asks why an acid-related molecule can treat a cholestatic autoimmune disease.

Lead-in: Which explanation is best?

A. OCA dissolves AMA immune complexes in bile ducts
B. OCA directly blocks IL-17 from autoreactive T cells
C. FXR agonism suppresses bile acid synthesis and modifies hepatocellular/cholangiocellular transporter expression, lowering toxic bile acid burden
D. OCA antagonizes mu-opioid receptors to treat only itch
E. OCA chelates copper and increases urinary excretion
Answer: C | Mechanism pearl: OCA is not an immunosuppressant; it exploits bile acid nuclear receptor feedback.

Question 112. cholestatic pruritus; PXR; opioid

A PBC patient on UDCA develops severe pruritus. Cholestyramine partially helps but interferes with levothyroxine. Rifampicin is tried, then naltrexone.

Lead-in: Which mechanism correctly pairs the drugs?

A. Cholestyramine activates PXR; rifampicin blocks mu-opioid receptors; naltrexone binds bile acids
B. Naltrexone suppresses CYP7A1 through FXR activation
C. Rifampicin directly increases AMA clearance through CD20 depletion
D. All three act by histamine H1 receptor blockade
E. Cholestyramine binds luminal bile acids; rifampicin activates PXR detoxification pathways; naltrexone antagonizes opioid receptors
Answer: E | Mechanism pearl: Cholestatic pruritus is multi-pathway; therapy is not just antihistamines.

Question 113. PSC; CCA; CA19-9

A man with IBD and PSC develops fever, jaundice, and a dominant extrahepatic stricture. CA19-9 is elevated during cholangitis, and brush cytology is atypical.

Lead-in: Which reasoning best avoids the common diagnostic trap?

A. Inflammation and obstruction can raise CA19-9, so cholangiocarcinoma requires integration of imaging, cytology/FISH, clinical course, and repeat assessment after drainage
B. Dominant strictures in PSC are always benign
C. CA19-9 alone is diagnostic of cholangiocarcinoma in PSC
D. Steroid response proves classic PSC rather than IgG4 disease
E. A normal bilirubin excludes malignancy in PSC
Answer: A | Mechanism pearl: PSC creates high CCA risk, but biomarkers are confounded by cholangitis and obstruction.

Question 114. IgG4 cholangitis; PSC mimic

A 42-year-old man has biliary strictures, pancreatic enlargement, salivary swelling, high IgG4, and dramatic biochemical improvement after steroids.

Lead-in: Which mechanism best differentiates this from PSC?

A. HBV-driven cccDNA persistence
B. HCV-driven IgM RF cryoglobulinemia
C. Genetic BSEP loss with low-GGT cholestasis
D. PDC-E2 autoimmune ductopenia with AMA positivity
E. Systemic IgG4-related fibroinflammatory disease with lymphoplasmacytic infiltration and steroid responsiveness
Answer: E | Mechanism pearl: IgG4-related cholangitis is a mimic; systemic organ pattern and steroid response are clues.

Question 115. PFIC2; BSEP

A neonate has progressive low-GGT cholestasis, normal extrahepatic ducts, severe pruritus, and ABCB11 mutation. Later he develops fibrosis.

Lead-in: Which mechanism best explains the liver injury?

A. **HFE** loss causes iron overload from **hepcidin** deficiency
B. **MDR3** loss removes phospholipid protection and primarily injures bile ducts with high GGT
C. Canalicular bile salt export failure causes intrahepatocyte bile acid retention and hepatocellular cholestatic injury
D. **UGT1A1** loss causes isolated unconjugated hyperbilirubinemia
E. **MRP2** loss causes benign conjugated hyperbilirubinemia without progressive cholestasis
Answer: C | Mechanism pearl: Low-GGT PFIC with **BSEP** defect is hepatocellular bile salt export failure.

Question 116. PFIC3; MDR3

A different child has high-GGT cholestasis, gallstones, and ABCB4/**MDR3** deficiency. Bile contains toxic unopposed bile salts with low phospholipid content.

Lead-in: Which mechanism explains the high-GGT cholangiopathy?

A. **CD81** activation expands **B cell**s
B. **Ferroportin** loss traps iron in **macrophage**s
C. Failure of phosphatidylcholine secretion removes detergent protection from bile acids, injuring cholangiocyte membranes
D. Loss of bilirubin conjugation prevents bile formation
E. Failure of bile salt export makes bile non-detergent and bland
Answer: C | Mechanism pearl: **MDR3** transports phospholipid into bile; without phospholipid, bile acids d**ama**ge ducts.

Question 117. ICP; bile acids

A 28-year-old pregnant woman at 34 weeks has intense pruritus, bile acids 110 µmol/L, mild ALT elevation, and normal ultrasound. Similar symptoms occurred in her mother during pregnancy.

Lead-in: Which mechanism best explains the syndrome?

A. Pregnancy hormones and genetic transporter susceptibility impair bile acid transport, causing maternal bile acid accumulation and fetal risk
B. Pregnancy causes anti-**PDC-E2** antibodies in all women
C. Copper cannot bind ceruloplasmin after 30 weeks gestation
D. IgM RF **immune complex**es deposit in the placenta
E. Fetal **HBV cccDNA** infects maternal cholangiocytes
Answer: A | Mechanism pearl: ICP is transporter/hormone biology; bile acid level is the key biomarker for risk stratification.

Question 118. DILI; HLA; immune

A 46-year-old woman develops severe hepatocellular injury 6 weeks after amoxicillin-clavulanate. She has fever, rash, eosinophilia, and cholestatic features. Viral and autoimmune workup is negative.

Lead-in: Which pathogenesis best fits idiosyncratic **DILI**?

A. Drug/metabolite-protein adducts plus **HLA**-restricted adaptive immune activation in a susceptible host
B. Dose-dependent direct **mitochondrial** toxicity in every exposed patient
C. **HCV** **CD81**-mediated cryoglobulin production
D. **FXR**-mediated physiologic suppression of bile acid synthesis
E. **ATP7B**-mediated copper accumulation
Answer: A | Mechanism pearl: Latency, immune features, and unpredictability are typical of idiosyncratic immune **DILI**.

Question 119. APAP; CYP2E1; glutathione

A malnourished alcohol user takes repeated supratherapeutic acetaminophen doses and presents late with AST 9000 U/L, INR 4.8, lactate elevation, and encephalopathy.

Lead-in: Which mechanism best explains vulnerability?

A. APAP produces cryoglobulins with low **C4**
B. Acetaminophen injury is primarily **IgG4** cholangitis
C. Alcohol prevents **NAPQI** formation completely
D. **CYP2E1** induction and low **glutathione** reserves increase **NAPQI**-mediated **mitochondrial** injury and necrosis
E. APAP causes **HFE**-mediated **hepcidin** deficiency
Answer: D | Mechanism pearl: Alcohol and malnutrition increase APAP risk through metabolism and detoxification capacity.

Question 120. ALF; ammonia; cerebral edema

A patient with acute liver failure develops agitation, rising **ammonia**, and signs of intracranial hypertension. **Lactulose** is not the central therapy in this setting.

Lead-in: Which pathophysiologic process is most important?

A. Rapid **ammonia** accumulation and systemic inflammation cause **astrocyte** swelling and cerebral edema before adaptive osmolyte compensation
B. Slow **manganese** accumulation in basal ganglia is the dominant acute mechanism
C. Bile acid pruritus pathways cause coma
D. Only **GABA-A** receptor activation matters; **ammonia** is irrelevant
E. **Portal hypertension** creates variceal shunting as the only driver
Answer: A | Mechanism pearl: ALF cerebral edema is rapid **astrocyte** osmotic stress, unlike chronic cirrhotic HE where adaptation is greater.

Question 121. Wilson ALF; copper

A 37-year-old woman presents with ALF, alkaline phosphatase disproportionately low relative to bilirubin, Coombs-negative hemolysis, and low ceruloplasmin. Kayser-Fleischer rings are seen.

Lead-in: Which mechanism best explains hemolysis and ALF?

A. **ATP7B** failure causes copper accumulation and sudden hepatocellular release, producing oxidative red-cell injury and hepatic necrosis
B. **BSEP** loss causes hemolysis by bile acid detergent injury to RBCs
C. **HCV** cryoglobulins cause isolated intravascular hemolysis
D. **HFE** loss causes acute hemolysis through iron overload
E. **PDC-E2** antibodies lyse red cells directly
Answer: A | Mechanism pearl: Wilson ALF is an exam classic: liver failure plus Coombs-negative hemolysis and copper toxicity.

Question 122. Wilson; D-penicillamine; zinc

An 18-year-old woman with **Wilson** disease and neurologic symptoms starts **D-penicillamine** and develops worsening tremor, then proteinuria. Her physician considers changing therapy.

Lead-in: Which mechanism-based explanation is most accurate?

A. Worsening neurologic disease proves the original diagnosis was hemochromatosis
B. Rapid copper mobilization may worsen neurologic symptoms, and **D-penicillamine** can cause immune renal toxicity; alternative chelation or **zinc** may be needed
C. Proteinuria proves copper excretion is therapeutic and should always be ignored
D. **D-penicillamine** acts only by inducing intestinal **metallothionein**
E. **Zinc** works by directly dissolving copper from basal ganglia
Answer: B | Mechanism pearl: Wilson treatment questions often test comparative pharmacology: chelators mobilize copper; **zinc** blocks absorption.

Question 123. hemochromatosis; hepcidin

A 44-year-old man has ferritin 1400 ng/mL, transferrin saturation 82%, diabetes, arthropathy, and hepatic iron predominantly in hepatocytes. **HFE** C282Y homozygosity is found.

Lead-in: Which mechanism explains the phenotype?

A. **PXR** activation increases iron absorption through CYP3A4
B. High **hepcidin** traps iron in **macrophage**s and lowers transferrin saturation
C. Low **hepcidin** relative to iron stores permits excessive **ferroportin**-mediated iron export from enterocytes and **macrophage**s into plasma
D. **MRP2** mutation prevents iron conjugation
E. **ATP7B** mutation causes iron export failure
Answer: C | Mechanism pearl: Classic **HFE** hemochromatosis is **hepcidin**-deficient iron loading with high transferrin saturation.

Question 124. ferroportin disease

A 39-year-old woman has high ferritin but normal transferrin saturation and iron-loaded **Kupffer cells**/**macrophage**s. Family history suggests autosomal dominant inheritance.

Lead-in: Which mechanism best explains the pattern?

A. **UGT1A1** deficiency causes **macrophage** iron deposition
B. **HFE** mutation causes low **macrophage** iron and very high transferrin saturation in all cases
C. **BSEP** mutation traps bile acids in **macrophage**s
D. **Ferroportin** loss-of-function prevents **macrophage** iron export, producing reticuloendothelial iron retention
E. Copper chelation failure blocks **macrophage** apoptosis

Answer: D | Mechanism pearl: Ferroportin disease can mimic iron overload but the cellular distribution and transferrin saturation differ.

Question 125. A1AT

A 51-year-old man with ZZ **alpha-1** antitrypsin deficiency has emphysema and cirrhosis. Liver biopsy shows PAS-positive diastase-resistant globules.

Lead-in: Which mechanism explains why liver and lung disease differ?

A. Bile acid transporter loss causes alveolar injury
B. Both liver and lung injury result from copper accumulation
C. A1AT deficiency directly suppresses **HBV cccDNA**
D. Misfolded **A1AT** polymer retention injures hepatocytes, while low circulating antiprotease activity predisposes lung elastin d**ama**ge
E. Hepatocytes overproduce **hepcidin** causing iron overload
Answer: D | Mechanism pearl: A1AT is a dual-mechanism disease: liver gain-of-toxic retention; lung loss-of-protective function.

Question 126. MASH; lipotoxicity; fibrosis

A 64-year-old man with metabolic syndrome has **MASH** cirrhosis. Biopsy shows ballooned hepatocytes, **Mallory-Denk** bodies, lobular inflammation, and perisinusoidal fibrosis.

Lead-in: Which sequence best explains progression?

A. BSEP overexpression generates toxic bile acid depletion
B. HCV CD81-mediated cryoglobulins deposit in hepatocytes
C. Insulin resistance and lipid oversupply generate lipotoxic stress, inflammatory cytokines, oxidative injury, stellate-cell activation, and fibrogenesis
D. Primary **AMA**-mediated duct destruction causes all **MASH** fibrosis
E. Low **AVP** causes renal sodium wasting and hepatic fibrosis
Answer: C | Mechanism pearl: MASH is metabolic-inflammatory liver injury; fibrosis is driven by stellate-cell activation after hepatocyte stress.

Question 127. MASH; fibrosis biomarkers

A **MASH** drug trial improves histology by reducing weight, improving **insulin resistance**, and decreasing hepatic inflammatory signaling. The examiner asks why fibrosis improvement often lags behind ALT improvement.

Lead-in: Which explanation is best?

A. Matrix degradation is independent of inflammatory activity
B. Fibrosis is caused only by bilirubin and changes immediately with ALT
C. ALT reflects active hepatocyte injury, whereas fibrosis requires matrix remodeling and stellate-cell i**nac**tivation over longer periods
D. ALT directly measures collagen content
E. Stellate cells cannot ever deactivate
Answer: C | Mechanism pearl: Biochemical response and architectural remodeling are different biologic endpoints.

Question 128. alcoholic hepatitis; steroids; infection

A patient with severe alcohol-associated hepatitis has high bilirubin, AST>ALT but both under 500, **neutrophil**ia, recent heavy drinking, and no biliary obstruction. Steroids are considered after infection is excluded.

Lead-in: Which mechanism makes infection exclusion especially important?

A. Corticosteroids suppress cytokine-driven inflammation but can worsen uncontrolled infection in a syndrome already linked to gut-derived **LPS** and innate immune activation
B. Steroids block **BSEP** and prevent bile flow
C. Steroids activate **HFE** and lower **hepcidin**
D. Steroids increase IgM RF cryoglobulin formation
E. Steroids directly chelate acetaldehyde from hepatocytes
Answer: A | Mechanism pearl: Alcoholic hepatitis is inflammatory but infection-prone; immunosuppression must be selected **car**efully.

Question 129. rebalanced hemostasis; PVT

A 57-year-old patient with advanced cirrhosis has spontaneous bruising, INR 2.1, platelets 55,000, high vWF, low protein C, and develops portal vein thrombosis.

Lead-in: Which concept best explains this apparent contradiction?

A. Protein C deficiency proves inherited thrombophilia only
B. High vWF prevents all clot formation
C. INR accurately measures both procoagulant and anticoagulant pathways
D. Cirrhosis creates fragile **rebalanced hemostasis**, not simple auto-anticoagulation; thrombosis can occur despite prolonged INR
E. Low platelets eliminate thrombin generation completely

Answer: D | Mechanism pearl: Advanced exam questions often test rejection of the 'auto-anticoagulated cirrhosis' myth.

Question 130. TIPS; HE; ascites

A cirrhotic patient with refractory ascites receives **TIPS**. Ascites improves, but he develops recurrent HE. Doppler confirms shunt patency.

Lead-in: Which mechanism best explains the tradeoff?

A. **TIPS** inhibits renal prostaglandins causing HE
B. **TIPS** removes all gut bacteria, causing nitrogen overload
C. Portal decompression improves sodium-retentive circulatory physiology but diverts **ammonia**-rich portal blood away from hepatocyte detoxification
D. **TIPS** directly d**ama**ges **astrocyte**s by mechanical embolization
E. **TIPS** blocks **V1 receptor**s and increases **C4** consumption
Answer: C | Mechanism pearl: TIPS is a hemodynamic solution with neurocognitive cost in susceptible patients.

Question 131. HPS; contrast echo

A 49-year-old woman with cirrhosis has dyspnea and platypnea. Oxygen saturation falls upright. Contrast echo shows bubbles in the left heart after several **car**diac cycles.

Lead-in: Which mechanism best explains hypoxemia?

A. Intrapulmonary vascular dilatation causes ventilation-perfusion mismatch and diffusion limitation in hepatopulmonary syndrome
B. Portal-vein thrombosis sends emboli to pulmonary arteries
C. **GABA-A** receptor activation reduces respiratory drive only
D. Pulmonary vascular remodeling increases pulmonary resistance like **POPH**
E. Atelectasis from ascites alone explains delayed bubbles
Answer: A | Mechanism pearl: Delayed bubble appearance suggests intrapulmonary shunting/dilatation, not intra**car**diac shunt.

Question 132. POPH; transplant

A transplant candidate with **portal hypertension** has exertional dyspnea. Right heart catheterization shows elevated mean pulmonary arterial pressure and high pulmonary vascular resistance.

Lead-in: Which pathobiology best explains why transplant may be unsafe until treated?

A. It is the same as hepatopulmonary syndrome and improves with oxygen alone
B. Portopulmonary hypertension reflects pulmonary arteriolar remodeling and vasoconstriction that can cause perioperative right-heart failure
C. It is caused by intrapulmonary vasodilatation with low resistance
D. It reflects **ammonia**-induced **astrocyte** swelling
E. It is a marker of isolated hypo**albumin**emia
Answer: B | Mechanism pearl: POPH is pulmonary arterial hypertension in **portal hypertension**; severity affects transplant candidacy.

Question 133. Budd-Chiari; JAK2

A patient with polycythemia vera and JAK2 positivity develops abdominal pain, ascites, hepatomegaly, and occlusion of hepatic veins. Liver biopsy shows centrilobular congestion.

Lead-in: Which mechanism is most central?

A. Direct **HCV** endothelial cytolysis causes necrotizing vasculitis
B. **BSEP** deficiency causes bile salt retention from birth
C. Hypercoagulability causes hepatic venous outflow obstruction with sinusoidal congestion and postsinusoidal **portal hypertension**
D. **UGT1A1** deficiency causes hepatomegaly
E. Autoimmune **PDC-E2** injury causes small duct loss
Answer: C | Mechanism pearl: Budd-Chiari questions often hide a myeloproliferative clue.

Question 134. SOS; transplant

A patient after hematopoietic stem-cell transplant develops painful hepatomegaly, rapid weight gain, jaundice, and ascites. Imaging does not show large hepatic vein thrombosis.

Lead-in: Which mechanism best explains the syndrome?

A. Conditioning-related sinusoidal endothelial injury causes sinusoidal obstruction and post-sinusoidal **portal hypertension**
B. **PBC** destroys interlobular bile ducts
C. **HFE**-related **hepcidin** deficiency acutely injures sinusoids
D. **IgG4** plasma-cell infiltration obstructs the common bile duct
E. Large-vessel hepatic vein thrombosis is required in every case

Answer: A | Mechanism pearl: Sinusoidal obstruction syndrome is microvascular endothelial injury, not always macroscopic hepatic vein clot.

Question 135. ischemic hepatitis; zone 3

A man with septic shock develops AST 6500 U/L and ALT 5800 U/L with rapid decline after perfusion improves. Bilirubin rises later and modestly.

Lead-in: Which pathophysiologic explanation is best?

A. Kupffer-cell iron overload causes all ischemic hepatitis
B. Hepatic **cccDNA** replication causes acute transaminase spikes
C. **Zone 3** hepatocytes undergo hypoxic injury because they are furthest from oxygen-rich periportal blood and rich in drug-metabolizing enzymes
D. Bile ducts necrose first because they lack arterial supply
E. Zone 1 hepatocytes are always most hypoxic
Answer: C | Mechanism pearl: Ischemic hepatitis is hemodynamic and zonal; values fall quickly when perfusion improves.

Question 136. congestive hepatopathy

A 58-year-old man with chronic right-sided heart failure has ascites with high protein, pulsatile hepatomegaly, and cholestatic liver tests. Cardiac imaging shows severe tricuspid regurgitation.

Lead-in: Which mechanism best explains his liver disease?

A. Hepatocytes cannot conjugate bilirubin due to **UGT1A1** mutation
B. **PDC-E2**-specific **AMA** destroys bile ducts
C. Splanchnic arterial vasodilatation is the sole initial defect
D. Transmission of venous pressure to hepatic sinusoids causes congestion, **zone 3** hypoxia, fibrosis, and portal hypertensive physiology
E. **HCV immune complex**es deposit in portal veins
Answer: D | Mechanism pearl: Congestive hepatopathy is pressure-backflow liver disease; ascitic protein is often high.

Question 137. HCC; imaging; AFP

A cirrhotic patient has a 2.1-cm lesion with arterial phase hyperenhancement and washout. AFP is 8 ng/mL. The radiology report calls it LI-RADS 5.

Lead-in: Which principle is most correct?

A. Biopsy is mandatory for every arterially enhancing nodule
B. Typical dynamic imaging can diagnose HCC in a cirrhotic liver even when AFP is normal
C. Normal AFP excludes HCC below 3 cm
D. Washout proves hemangioma rather than HCC
E. **DCP** must be elevated before imaging diagnosis
Answer: B | Mechanism pearl: HCC diagnosis is imaging-pattern based in the right risk context; AFP is imperfect.

Question 138. HCC; sorafenib

A patient with advanced HCC begins **sorafenib**. He develops hand-foot skin reaction and hypertension, while imaging shows disease stabilization rather than tumor disappearance.

Lead-in: Which mechanism best explains expected antitumor effect?

A. Inhibition of **RAF**/MEK/ERK proliferation signaling and **VEGF**R/**PDGFR**-mediated angiogenesis
B. Chelation of copper from malignant hepatocytes
C. Activation of **FXR** to suppress **CYP7A1**
D. Covalent binding to **AFP-L3** glycoforms
E. Direct immune checkpoint blockade of **PD-1** only
Answer: A | Mechanism pearl: Targeted HCC therapies may stabilize angiogenic tumors without dramatic shrinkage.

Question 139. transplant; sirolimus; HCC

A post-transplant patient with prior HCC is considered for **sirolimus** rather than **calcineurin**-inhibitor-heavy immunosuppression.

Lead-in: Which mechanistic rationale supports this strategy?

A. **mTOR** inhibition suppresses lymphocyte proliferation and may reduce tumor cell growth/angiogenesis signaling
B. **Sirolimus** antagonizes **ammonia** at **NMDA** receptors
C. **Sirolimus** directly blocks **HBV** reverse transcription
D. **Sirolimus** increases **IL-2** transcription more than **tacrolimus**
E. **Sirolimus** activates **BSEP** and eliminates cholestasis
Answer: A | Mechanism pearl: **mTOR** links immune proliferation and cancer biology; this creates a translational rationale in selected HCC patients.

Question 140. tacrolimus; calcineurin

A transplant recipient develops tremor, hypertension, hyperkalemia, and nephrotoxicity on **tacrolimus**. Liver enzymes are stable.

Lead-in: Which pathway is being inhibited?

A. **FXR**/RXR bile acid transcriptional feedback
B. **Calcineurin**-dependent NFAT activation and **IL-2** transcription
C. **mTOR**-dependent protein translation downstream of **IL-2** receptor
D. **TSPO**-mediated neurosteroid synthesis
E. **CYP2E1** conversion of acetaminophen to **NAPQI**
Answer: B | Mechanism pearl: Tacrolimus toxicity is common; mechanism remains **calcineurin** blockade upstream of **IL-2**.

Question 141. cholestatic pruritus

A patient with chronic cholestasis has severe pruritus but only modest bilirubin elevation. Antihistamines fail. The fellow says itch must be histamine-mediated because there is scratching.

Lead-in: Which response is most mechanistic?

A. Pruritus severity directly measures bilirubin concentration
B. Histamine is the only mediator of cholestatic pruritus
C. Cholestatic itch involves nonhistamine mediators, altered bile acid/autotaxin-related signaling and endogenous opioidergic tone; antihistamines mainly sedate
D. **Hepcidin** deficiency causes cholestatic itch
E. **GABA-A** antagonists are first-line treatment
Answer: C | Mechanism pearl: Exam questions often separate pruritus biology from bilirubin level and histamine.

Question 142. cholestasis; transporters

A patient with cholestatic liver injury has increased intracellular bile acids. Molecular profiling shows decreased basolateral uptake and increased basolateral export transporters.

Lead-in: Which adaptive logic best explains these findings?

A. Hepatocytes increase uptake to maximize canalicular pressure
B. These changes prove autoimmune hepatitis
C. This adaptation is mediated only by **GABA-A** receptors
D. Hepatocytes reduce further bile acid entry and shunt bile acids back to blood to limit intracellular detergent injury
E. The purpose is to increase copper incorporation into ceruloplasmin
Answer: D | Mechanism pearl: Cholestasis triggers nuclear receptor-guided transporter adaptation: less uptake, more alternative efflux.

Question 143. HBV; cccDNA; tenofovir

A patient with chronic hepatitis B and family history of HCC has low viral load on tenofovir but remains HBsAg positive. He asks why treatment must continue for years.

Lead-in: Which mechanism is the best explanation?

A. Tenofovir only neutralizes circulating HBsAg but not **HBV** DNA
B. **HBV** replicates only inside **B cell**s through **CD81**
C. HBsAg persistence proves poor adherence in every case
D. Nucleos(t)ide analogues suppress reverse transcription but do not reliably eradicate **cccDNA** or all HBsAg-producing templates
E. **HBV** uses **NS5A**, requiring lifelong **NS5A** inhibition
Answer: D | Mechanism pearl: HBV functional cure is hard because of stable nuclear **cccDNA** and antigen persistence.

Question 144. HDV; HBV

A patient with chronic **HBV** acquires **HDV** and rapidly progresses to cirrhosis. The examiner asks why **HDV** cannot be managed as an independent infection.

Lead-in: Which mechanism is correct?

A. **HDV** uses **HBV** polymerase for genome replication
B. **HDV** cannot infect hepatocytes expressing **NTCP**
C. **HDV** is a DNA virus integrated into **cccDNA**
D. **HDV** replication uses its own RNA strategy but requires **HBV** surface antigen for assembly and transmission
E. **HDV** is eradicated by **rifaximin** through gut decontamination
Answer: D | Mechanism pearl: HDV dependence on HBsAg makes **HBV** envelope biology central to disease control.

Question 145. NSAIDs; cirrhosis; renal prostaglandins

A patient with advanced cirrhosis develops AKI after NSAID use. Previously he had stable ascites.

Lead-in: Which mechanism best explains the precipitous renal decline?

A. NSAIDs block hepatic **cccDNA** and trigger **immune complex** nephritis
B. NSAID inhibition of renal prostaglandins removes a compensatory vasodilator system maintaining renal perfusion against **RAAS**/**SNS**/**AVP** tone
C. NSAIDs improve renal **nitric oxide** and cause hyperfiltration injury
D. NSAIDs bind **albumin** and raise oncotic pressure excessively
E. NSAIDs directly activate **V1 receptor**s in splanchnic arteries
Answer: B | Mechanism pearl: Renal prostaglandins are protective in cirrhosis; NSAIDs can precipitate renal failure.

Question 146. paracentesis; albumin

A patient with decompensated cirrhosis has large-volume paracentesis without **albumin** and then develops hypotension, hyponatremia, and renal dysfunction.

Lead-in: Which mechanism best explains post-paracentesis circulatory dysfunction?

A. Albumin is only antibacterial and unrelated to hemodynamics
B. Ascitic fluid removal increases portal vein thrombosis in every patient
C. Paracentesis directly destroys renal tubules
D. Rapid reduction in intra-abdominal/vascular effective volume worsens arterial underfilling, activating vasoconstrictor and water-retaining systems
E. Paracentesis causes **HBV** reactivation
Answer: D | Mechanism pearl: Albumin after large-volume paracentesis prevents circulatory dysfunction by supporting effective volume.

Question 147. DCP; HCC biomarker

A patient with cirrhosis and HCC has high **DCP** but is on warfarin and has vitamin K deficiency from cholestasis.

Lead-in: Which interpretation is most sophisticated?

A. DCP proves portal vein thrombosis rather than tumor
B. DCP reflects abnormal prothrombin **car**boxylation and may be confounded by vitamin K antagonism or deficiency, so it requires clinical context
C. DCP is unaffected by vitamin K biology
D. DCP is identical to **AFP-L3** and cannot be confounded
E. DCP is diagnostic of **cholangiocarcinoma** only
Answer: B | Mechanism pearl: Biomarker biology prevents overinterpretation: **DCP**/PIVKA-II is tied to prothrombin **car**boxylation.

Question 148. ACLF; systemic inflammation

A cirrhotic patient with severe bacterial infection develops **ACLF** with shock, renal failure, HE, and very high inflammatory markers. His baseline MELD was modest before infection.

Lead-in: Which explanation best describes the transition?

A. ACLF is explained by normal INR in cirrhosis
B. Systemic inflammation and immune-metabolic dysregulation trigger multiorgan failure beyond baseline hepatic synthetic dysfunction
C. ACLF is merely a slow rise in bilirubin without inflammation
D. ACLF occurs only after variceal bleeding and never infection
E. ACLF requires congenital transporter disease
Answer: B | Mechanism pearl: ACLF is an acute inflammatory organ-failure syndrome on chronic liver disease.

Question 149. portal hypertension; statins; NO

A trial enrolls patients with cirrhosis and **portal hypertension** using statins to improve endothelial function. The endpoint includes **HVPG** and decompensation.

Lead-in: Which mechanism gives the strongest rationale?

A. Statins eliminate **cccDNA** from **HBV**-infected hepatocytes
B. Statins are V1 agonists identical to **terlipressin**
C. Statins may increase endothelial **nitric oxide** signaling and reduce intrahepatic vascular resistance while exerting anti-inflammatory/antifibrotic effects
D. Statins bind bile acids in the intestinal lumen like **cholestyramine**
E. Statins directly ligate varices mechanically
Answer: C | Mechanism pearl: Some **portal hypertension** strategies target dynamic endothelial/stellate-cell components, not only portal inflow.

Question 150. PBC; fatigue; transplant

A woman with **PBC** has fatigue, pruritus, xanthelasma, ALP elevation, and **AMA** positivity. Her bilirubin is normal and elastography suggests early-stage disease. She wants transplant because fatigue is disabling.

Lead-in: Which reasoning is best?

A. Normal bilirubin excludes all symptoms from **PBC**

B. Fatigue can be severe but is poorly linked to hepatic failure severity; transplant decisions rely on objective liver failure or intractable complications rather than fatigue alone

C. Fatigue alone is equivalent to MELD decompensation

D. **AMA** titer directly determines transplant priority

E. **UDCA** is contraindicated when fatigue is prominent

Answer: B | Mechanism pearl: **PBC** symptoms and prognosis diverge; bilirubin, ALP response, fibrosis, **portal hypertension**, and complications drive staging.

Compact Answer Key

Q - Answer	Q - Answer	Q - Answer	Q - Answer	Q - Answer
1: A	31: A	61: D	91: E	121: A
2: A	32: E	62: A	92: E	122: B
3: A	33: D	63: A	93: B	123: C
4: C	34: E	64: D	94: C	124: D
5: C	35: D	65: B	95: C	125: D
6: B	36: E	66: B	96: E	126: C
7: C	37: C	67: C	97: E	127: C
8: E	38: D	68: C	98: D	128: A
9: A	39: B	69: D	99: A	129: D
10: C	40: D	70: C	100: D	130: C
11: A	41: E	71: C	101: A	131: A
12: A	42: B	72: D	102: A	132: B
13: B	43: D	73: E	103: D	133: C
14: B	44: A	74: E	104: C	134: A
15: A	45: D	75: C	105: C	135: C
16: B	46: D	76: E	106: A	136: D
17: D	47: B	77: B	107: E	137: B
18: A	48: E	78: E	108: C	138: A
19: D	49: D	79: B	109: E	139: A
20: E	50: E	80: C	110: B	140: B
21: B	51: E	81: E	111: C	141: C
22: A	52: A	82: B	112: E	142: D
23: E	53: E	83: D	113: A	143: D
24: D	54: B	84: C	114: E	144: D
25: D	55: D	85: D	115: C	145: B
26: D	56: B	86: B	116: C	146: D
27: C	57: E	87: A	117: A	147: B
28: B	58: B	88: E	118: A	148: B
29: E	59: E	89: B	119: D	149: C
30: C	60: D	90: C	120: A	150: B

Source Use Note

The questions are newly written and not copied from source MCQs. Source material was used for factual scaffolding and mechanism validation, especially: **portal hypertension**/HRS/HE, cholestatic nuclear receptor and transporter biology, viral hepatitis, **HCV cryoglobulinemia**, **DILI**, autoimmune liver disease, **MASLD**/**MASH**, alcoholic hepatitis, metabolic liver disease, vascular liver disease, HCC biomarkers and targeted therapy, and transplant immunopharmacology.