

Drug- and Toxin-Induced Liver Injury

Pathogenesis • morphologic patterns • clinicopathologic diagnosis

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Learning outcomes

- Distinguish dose-dependent toxicity from idiosyncratic reactions.
- Link reactive metabolites, hepatic zonation, and hepatocellular necrosis.
- Recognize the principal histologic patterns of injury.
- Integrate exposure chronology, laboratory phenotype, and exclusion of competing causes.

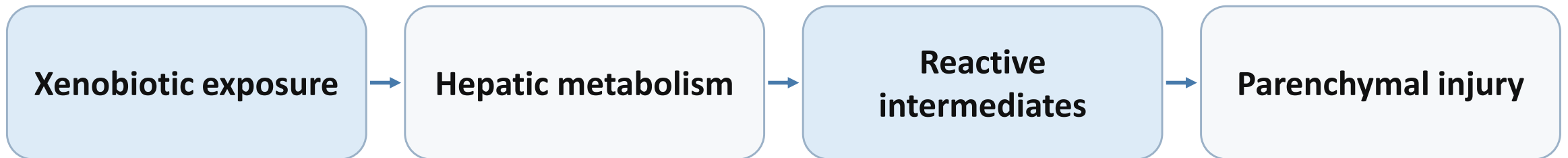
DILI is a clinicopathologic diagnosis

- Drug-induced liver injury (DILI) encompasses hepatic injury due to medications and other xenobiotics.
- The same exposure may create more than one histologic or biochemical pattern.
- Neither the presenting symptoms nor the biopsy appearance is individually pathognomonic.

Diagnosis requires exposure chronology and exclusion of alternatives.

Why the liver is especially vulnerable

- Portal inflow delivers absorbed xenobiotics to hepatocytes.
- Hepatic biotransformation may detoxify compounds or generate toxic intermediates.
- Compartment-specific enzyme activity helps determine the distribution of injury.



The clinical burden extends beyond acute hepatitis

- DILI as a major cause of acute liver failure in the United States.
- Among patients in the cited US DILIN cohort, 10% died or required transplantation.
- In that cohort, 17% developed chronic liver disease.

10% Death or transplantation

17% Chronic liver disease

Cohort outcomes reported; Not the risk for every exposed patient.

Potential hepatotoxins extend beyond prescriptions

- Prescription and nonprescription medicines.
- Herbal products and nutritional supplements.
- Poisonous plants and fungi, including Amanita mushrooms.
- Household or industrial chemicals, including solvents and pesticides.

Medicines

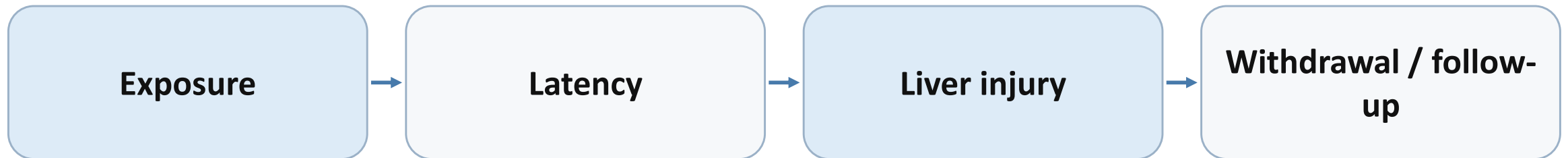
Supplements

Plants & fungi

Chemicals

The exposure-to-injury interval varies

- Toxic injury may become apparent soon after exposure.
- Other reactions emerge after weeks or months.
- A convincing assessment must reconstruct the onset, duration, and cessation of all suspected exposures.



Two broad mechanisms organize DILI

Intrinsic toxicity

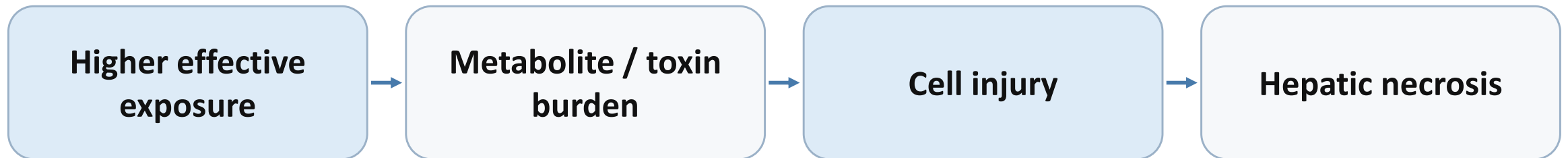
- Dose-dependent
- Often acute
- Acetaminophen is classic

Idiosyncratic injury

- Unpredictable
- Often delayed
- May involve immune or host factors

Intrinsic injury: Dose predicts risk

- In direct toxicity, the exposure or its toxic metabolite injures hepatocytes.
- Acetaminophen is the classical example.
- Other direct hepatotoxins cited include organic solvents and mushroom toxins.



Idiosyncratic injury: Host susceptibility matters

- Most drug-induced injury described in this section is idiosyncratic.
- Only a minority of exposed individuals develop the reaction.
- A typical latency of one to three months is described, although individual presentations vary.

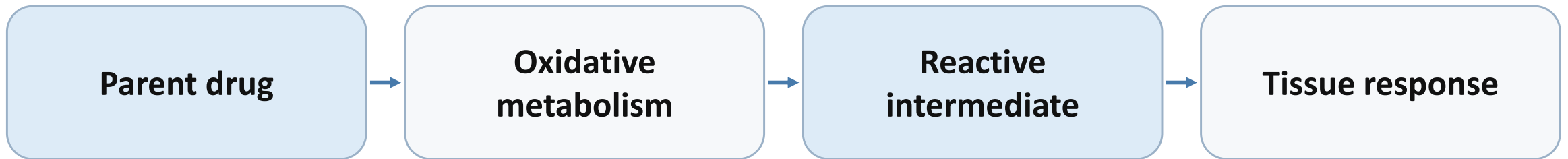
A therapeutic dose does not exclude a serious idiosyncratic reaction.

Contrasting the intrinsic and idiosyncratic patterns

Feature	Intrinsic	Idiosyncratic
Predictability	Relatively predictable	Unpredictable
Dose relationship	Characteristic	Not simply dose-dependent
Example	Acetaminophen	Many antimicrobials
Histology	Often necrosis dominant	Often hepatitis-like

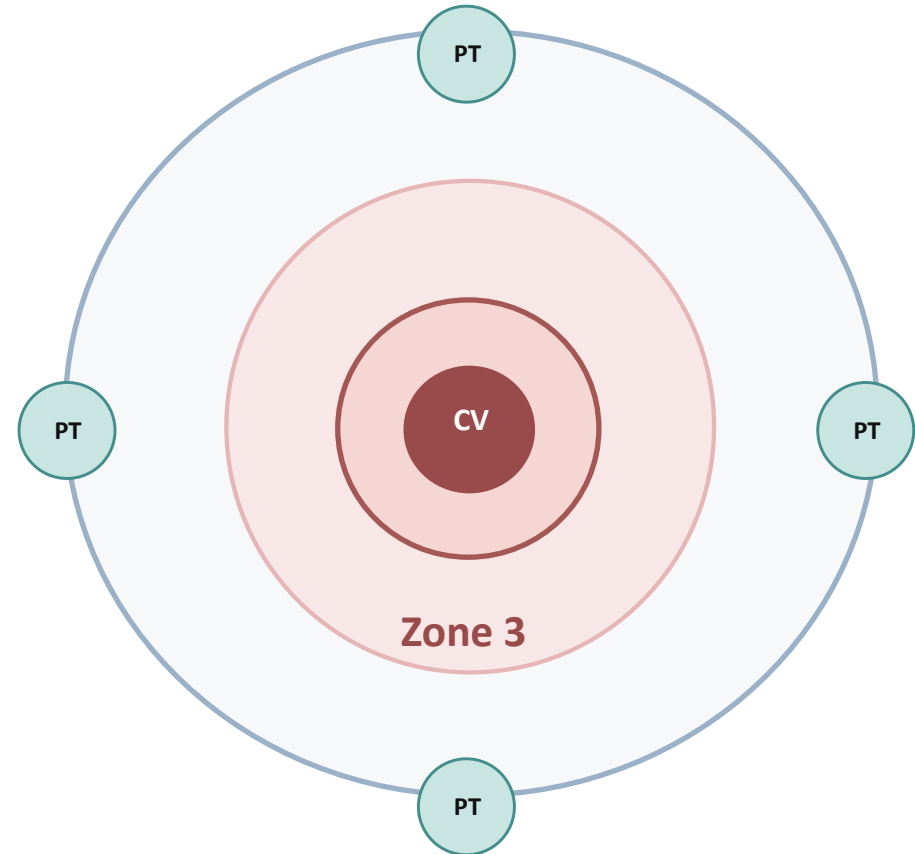
Reactive metabolites can initiate tissue injury

- Hepatocytes enzymatically convert many parent compounds to intermediates.
- Some intermediates are more reactive than the parent drug.
- Downstream effects may include cell damage, inflammation, or necrosis.



Cytochrome P450 links metabolism to zonal injury

- Cytochrome P450 enzymes mediate many xenobiotic reactions.
- Higher metabolic activity in the centrilobular region.
- Perivenular (zone 3) necrosis is therefore a recurring morphologic clue.

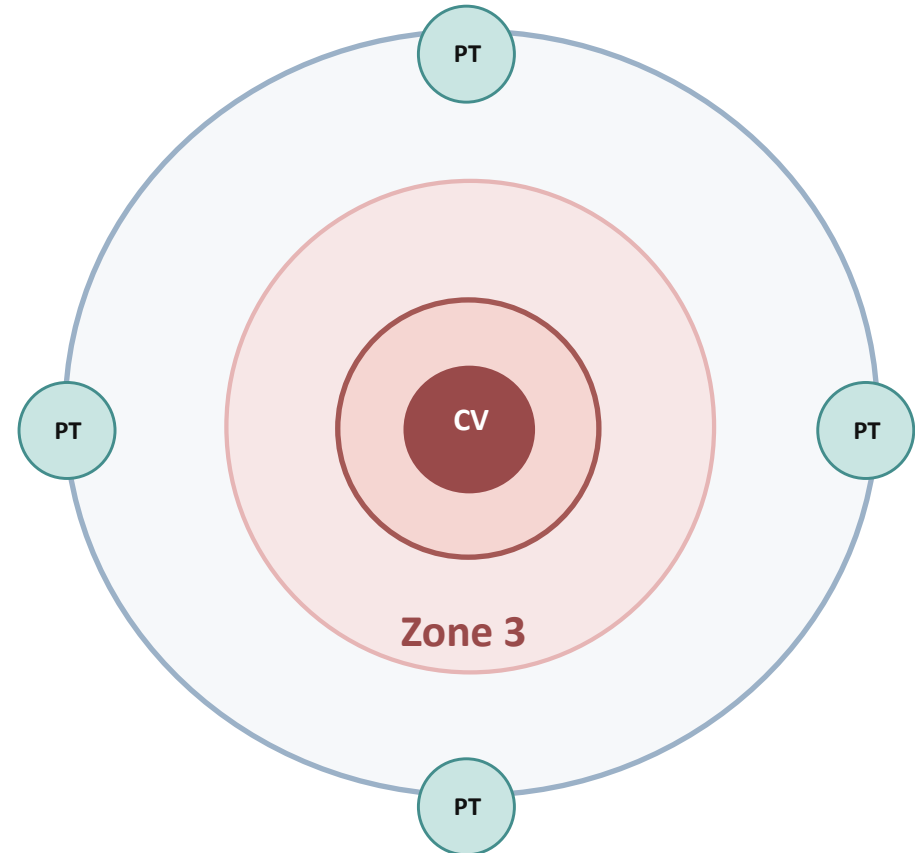


PT: Portal tract • CV: Central vein

Simplified hepatic lobule: Periportal to perivenular gradient.

Zone 3 necrosis reflects metabolic geography

- Centrilobular and perivenular identify the region nearest a terminal hepatic venule.
- Metabolic activation of some xenobiotics is particularly important in this zone.
- Zonal necrosis supports a mechanism but does not uniquely establish DILI.

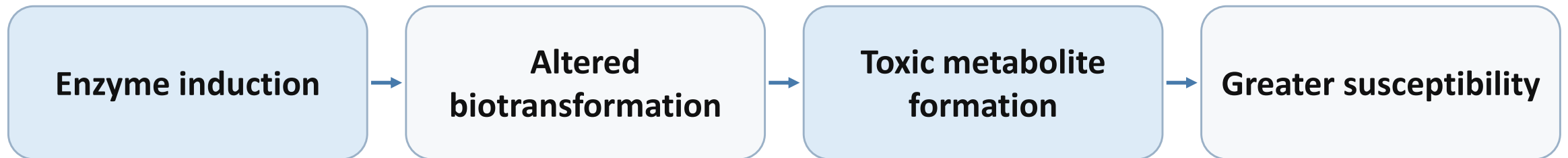


PT: Portal tract • CV: Central vein

Schematic topography; Not a histologic photomicrograph.

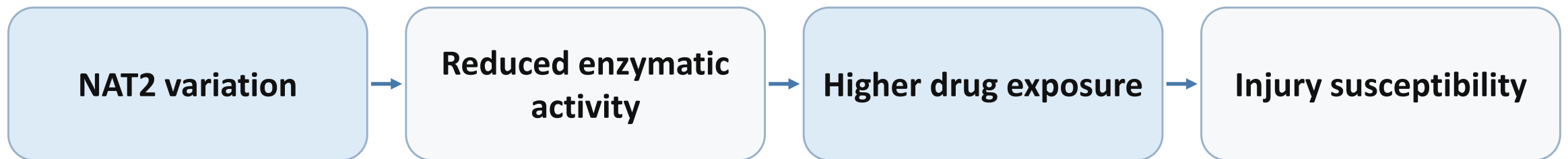
Enzyme induction may amplify co-exposure toxicity

- Rifampicin, phenytoin, isoniazid, tobacco smoke, and ethanol as enzyme-inducing exposures.
- Induction can alter formation of reactive metabolites from another compound.
- Clinical interpretation must consider combinations rather than one drug in isolation.



Genetic metabolism affects susceptibility

- NAT2 variation as one contributor to isoniazid hepatotoxicity.
- Reduced N-acetyltransferase activity can increase hepatic exposure to relevant compounds.
- A genetic predisposition does not imply inevitable injury in every carrier.



Immune mechanisms contribute to some reactions

- Some idiosyncratic reactions are thought to involve hypersensitivity to drugs or their metabolites.
- An inflammatory pattern may include lymphocytes, eosinophils, and plasma cells.
- These features suggest a reaction pattern but are not specific for an individual drug.

An inflammatory infiltrate is not proof of drug causality.

Antimicrobials are prominent idiosyncratic culprits

- The textbook attributes nearly half of idiosyncratic cases to antimicrobial agents.
- Examples across its pattern table include antibiotics and isoniazid.
- Associated lesions range from hepatitis to cholestatic injury or granulomas.

Acute hepatitis

Cholestatic hepatitis

Granulomas

Chronic hepatitis

Many therapeutic classes may injure the liver

- The implicated classes include cardiovascular drugs, CNS drugs, antineoplastic agents, and NSAIDs.
- Immune-checkpoint inhibitors such as PD-1/PD-L1/CTLA-4 agents are also included.
- Drug class alone cannot predict the histologic pattern in an individual patient.

Cardiovascular

CNS agents

Oncology

Analgesics / NSAIDs

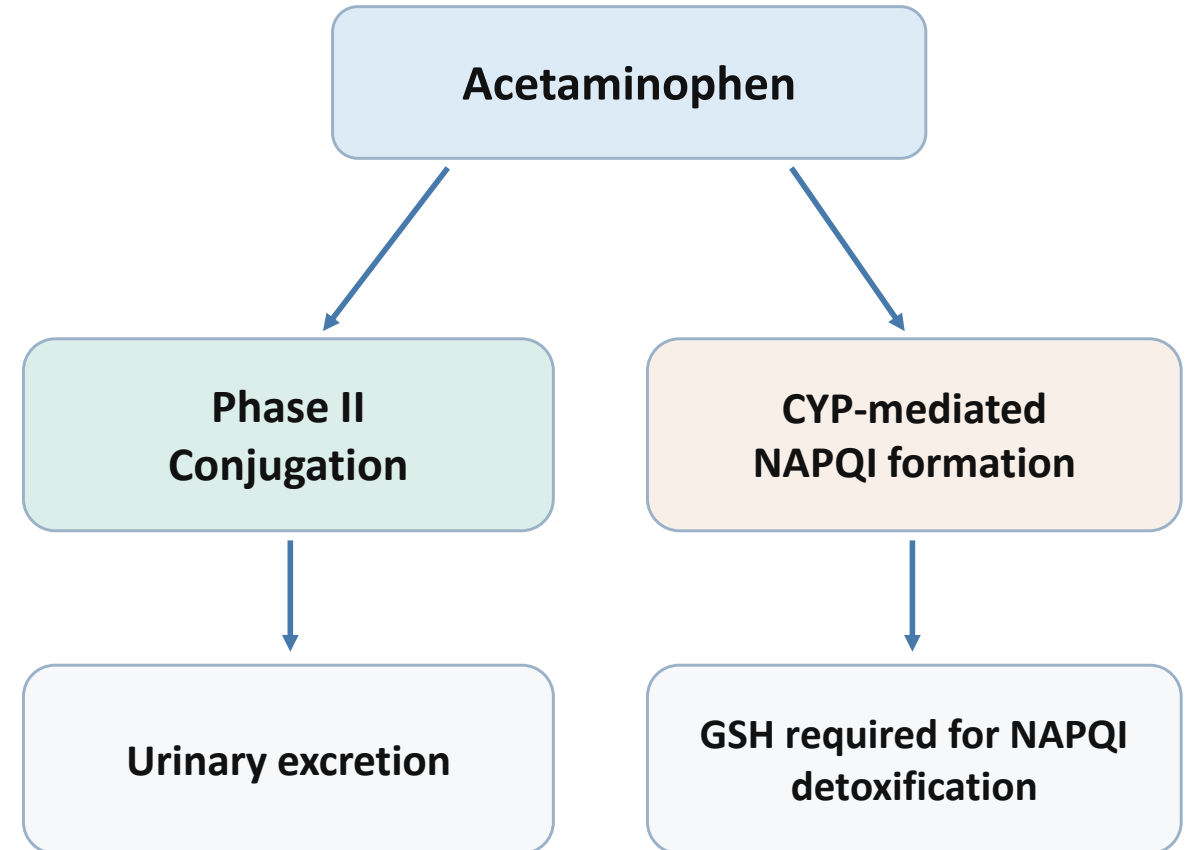
Supplements and environmental exposures require explicit inquiry

- Herbal and nutritional products are implicated in idiosyncratic injury.
- Patients may not spontaneously report nonprescription or traditional preparations.
- Fungal toxins, solvents, and industrial exposures broaden the differential.

Record every ingested, inhaled, and occupational exposure.

Acetaminophen provides the model of intrinsic injury

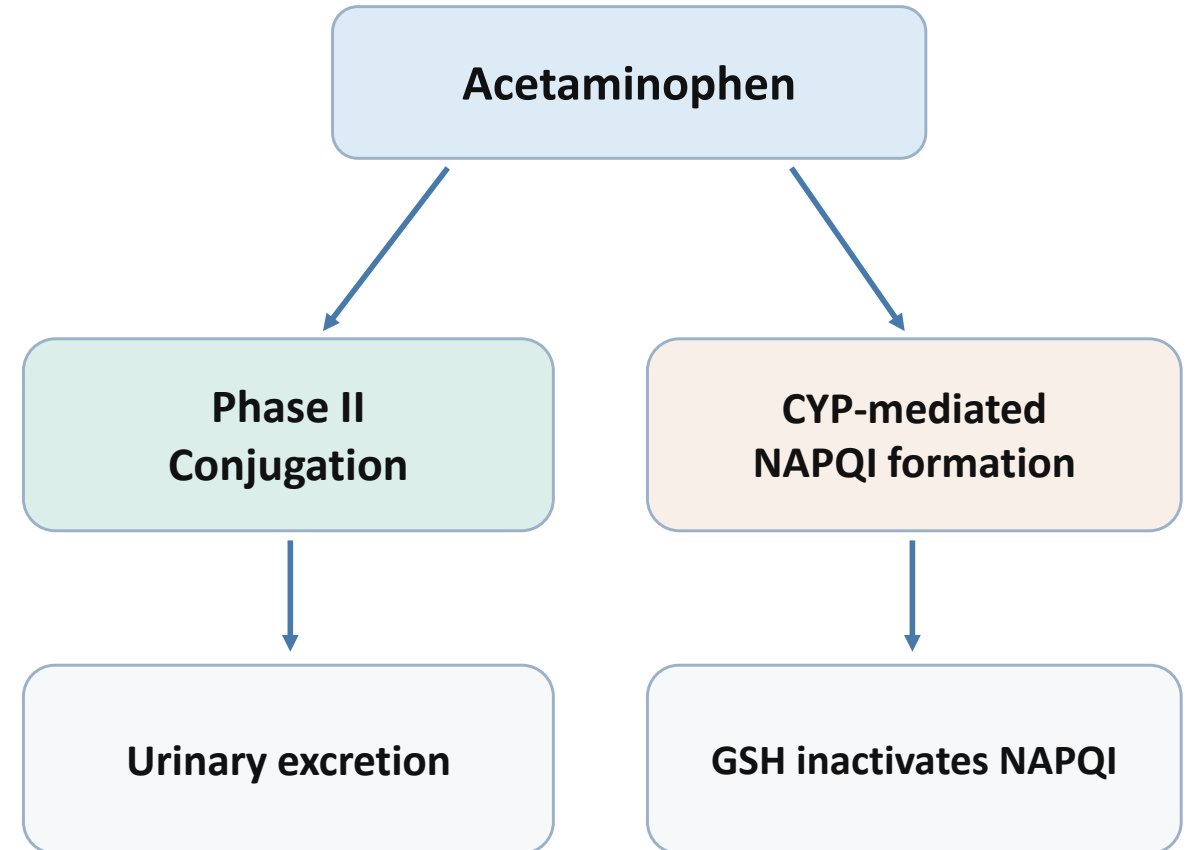
- At therapeutic exposure, the major fraction is detoxified by phase II metabolism.
- A small fraction undergoes cytochrome-dependent formation of NAPQI.
- Normally, glutathione conjugates and inactivates NAPQI.



Original editable metabolic pathway schematic.

Glucuronidation and sulfation are protective

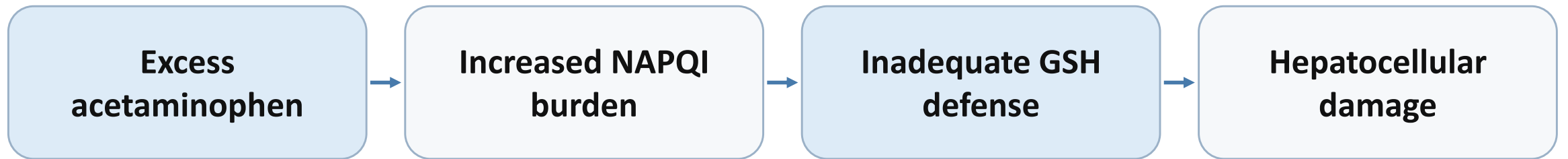
- Glucuronide and sulfate conjugation as the major metabolic pathway.
- These water-soluble conjugates permit urinary elimination.
- A smaller oxidative pathway generates NAPQI and requires glutathione detoxification.



Original editable metabolic pathway schematic.

Overdose shifts the NAPQI balance

- With excessive acetaminophen, the burden of reactive NAPQI increases.
- Glutathione stores are depleted or insufficient to detoxify the accumulated metabolite.
- Unconjugated NAPQI promotes hepatocyte injury.



Protein adducts and oxidative stress mediate toxicity

- NAPQI binds covalently to hepatic proteins.
- Mitochondrial dysfunction contributes to cellular damage.
- Depletion of glutathione increases susceptibility to reactive oxygen species.

**NAPQI–protein
adducts**

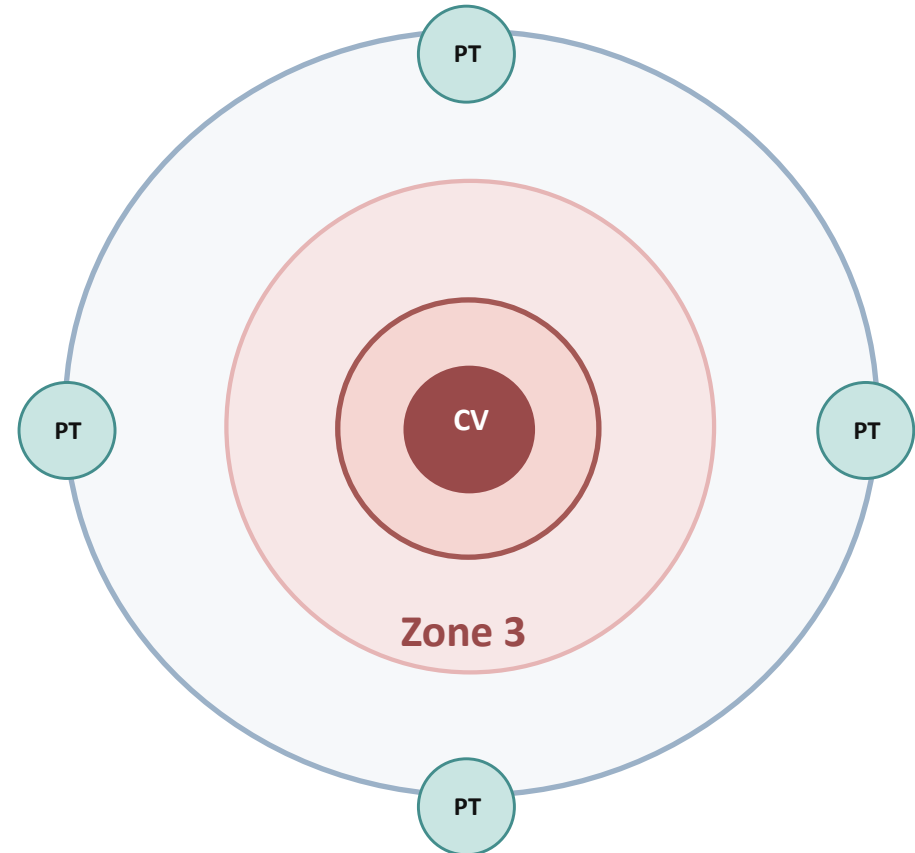
Mitochondrial damage

GSH depletion

Oxidative injury

Acetaminophen injury preferentially affects zone 3

- Centrilobular hepatocytes are vulnerable to metabolic activation of acetaminophen.
- The source describes confluent perivenular necrosis, sometimes extending across lobules.
- Inflammation may be relatively limited compared with extensive necrosis.



PT: Portal tract • CV: Central vein

Schematic distribution of necrosis, not a tissue section.

Necrosis-dominant injury differs from hepatitis-dominant injury

Necrosis dominant

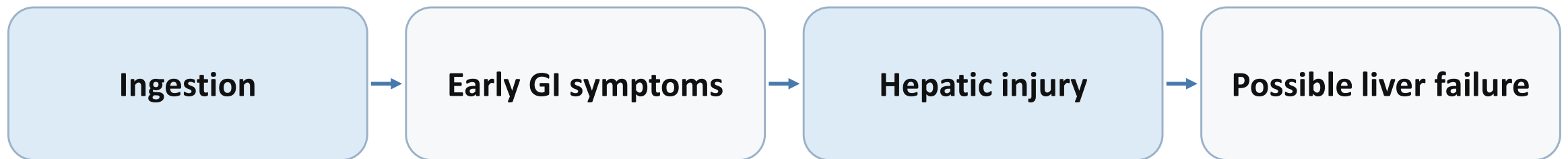
- Confluent cell loss
- Sparse infiltrate
- Acetaminophen; Halothane

Inflammation dominant

- Lymphocytes $\pm$ other cells
- Variable single-cell necrosis
- Many antimicrobials

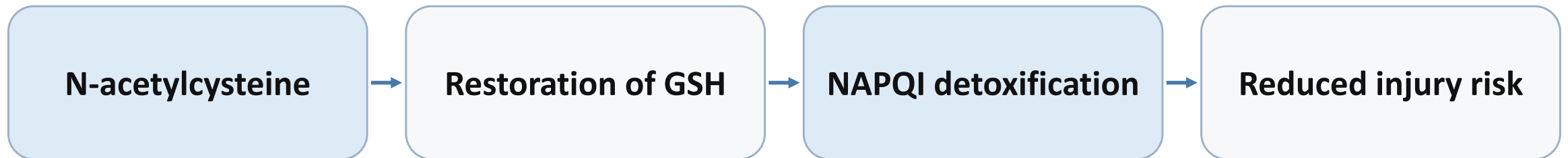
Acetaminophen poisoning evolves clinically

- Early complaints may include nausea, vomiting, or diarrhea.
- A subsequent interval can be followed by jaundice and biochemical evidence of hepatic injury.
- Severe intoxication can progress to acute liver failure.



N-acetylcysteine targets the detoxification deficit

- N-acetylcysteine as a therapy that restores glutathione.
- Early administration is particularly beneficial.
- Clinical management must not be delayed by an apparently mild initial presentation.



Severe intrinsic toxicity can involve other organs

- Acetaminophen poisoning may lead to acute liver failure.
- The textbook also notes concurrent renal injury in some patients.
- Widespread hepatocellular necrosis can require transplantation.

A hepatotoxin may produce systemic or multiorgan consequences.

Direct-acting toxins are not limited to acetaminophen

- Organic solvents can cause severe liver injury.
- Certain poisonous mushrooms contain potent hepatic toxins.
- Exposure reconstruction must include environmental and dietary sources.

Acetaminophen

Organic solvents

Toxic mushrooms

Other xenobiotics

The biopsy vocabulary spans multiple patterns

- Patterns described include hepatitic, cholestatic, steatotic, vascular, granulomatous, fibrosing, and neoplastic alterations.
- The histologic reaction may combine several patterns in one biopsy.
- Morphology characterizes the injury but cannot independently identify its cause.

Hepatitic

Cholestatic

Steatotic

Vascular / other

Three major clinical-biochemical patterns

Hepatocellular

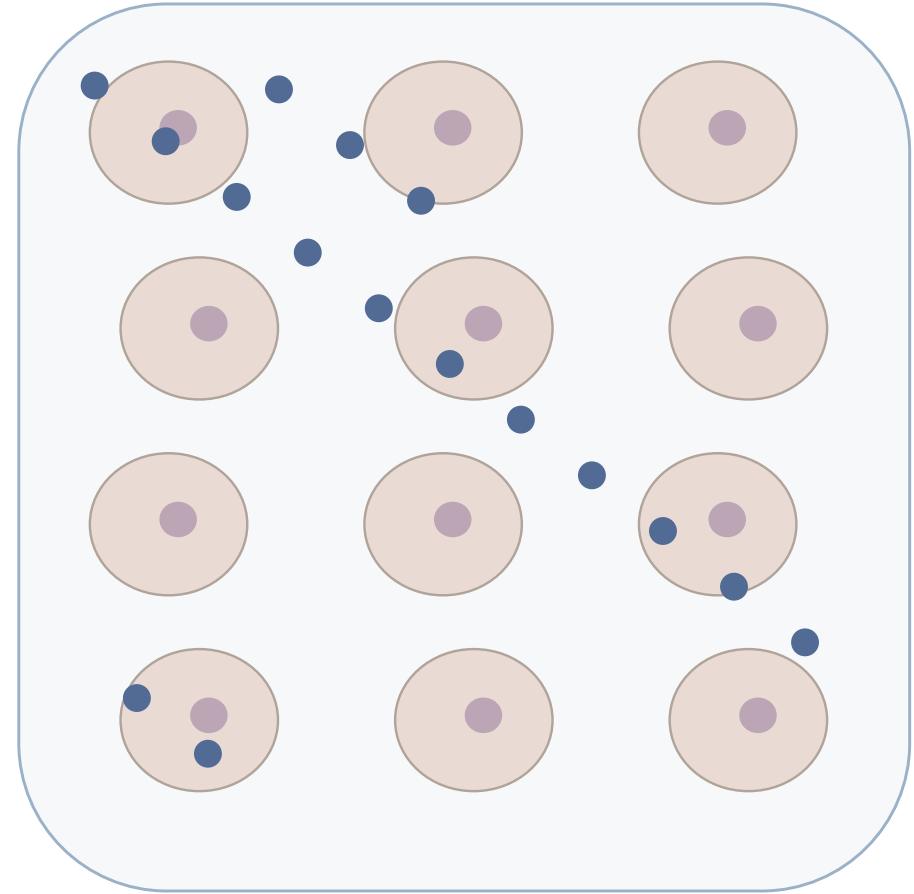
- ALT-predominant
- Hepatitis-like injury
- Necrosis may be present

Cholestatic / mixed

- ALP-predominant or dual
- Bile accumulation / duct injury
- Ductular reaction may occur

Acute hepatitis: Inflammation dominates

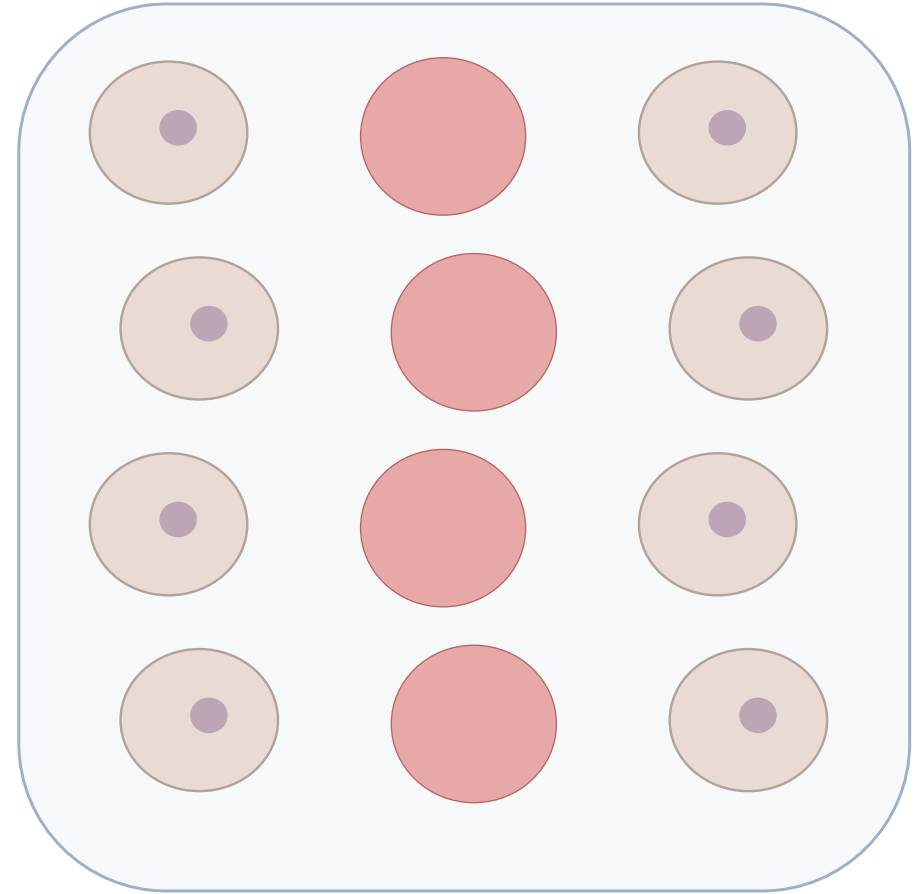
- Lobular lymphocytic inflammation is conspicuous.
- Plasma cells and eosinophils may be present in variable proportions.
- Single-cell necrosis or confluent necrosis may accompany the infiltrate.



Schematic inflammatory pattern; Not an H&E section.

Acute hepatitis: Necrosis dominates

- Confluent hepatocyte necrosis is the major abnormality.
- Inflammation may be relatively sparse.
- The textbook associates this pattern with acetaminophen and halothane.



Schematic hepatocyte loss; Not an H&E section.

DILI can resemble viral or autoimmune hepatitis

Potentially shared features

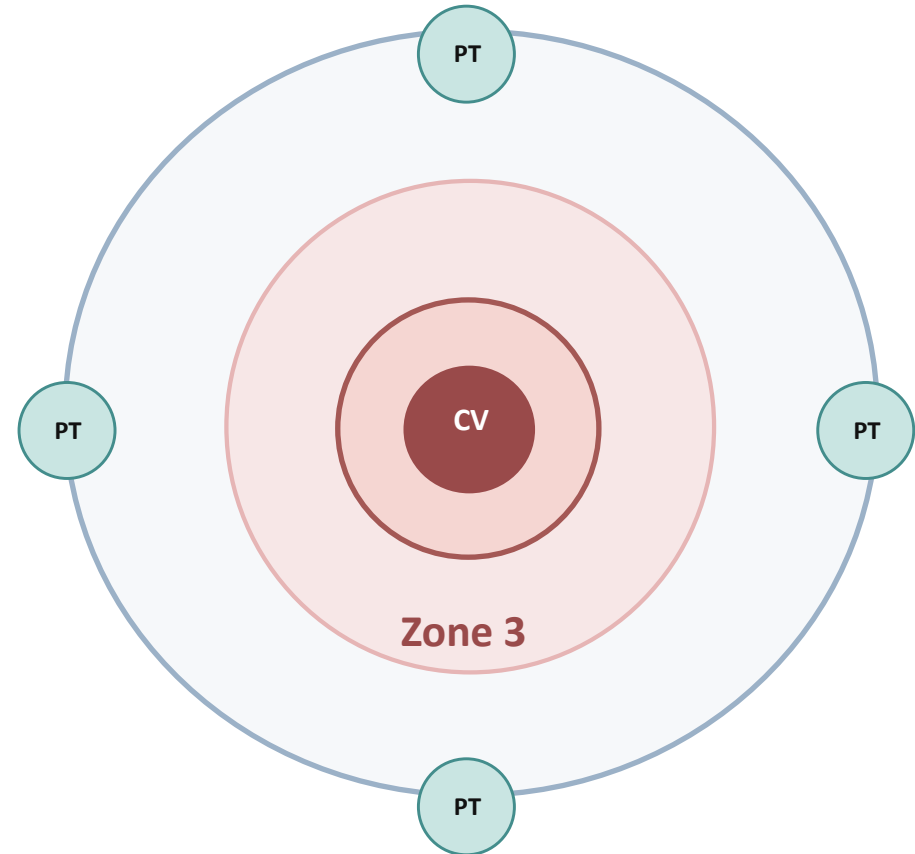
- Interface / lobular activity
- Plasma cells or eosinophils
- Hepatocyte necrosis

Needed to attribute DILI

- Credible exposure chronology
- Competing-cause work-up
- Trajectory after withdrawal

Centrizonal accentuation is useful but nonspecific

- In the hepatitic pattern, injury may cluster near terminal hepatic venules.
- The source identifies centrizonal necrosis as a common feature.
- It cannot distinguish every medication reaction from other causes of zonal injury.

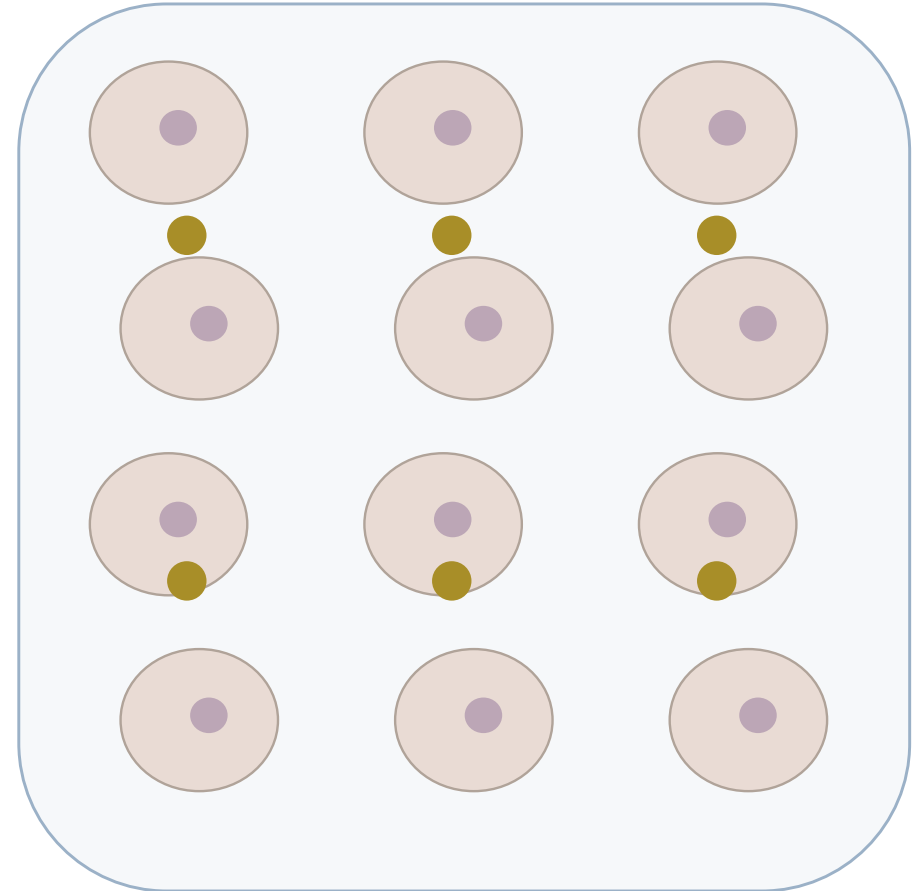


PT: Portal tract • CV: Central vein

Schematic zonation.

Bland hepatocellular cholestasis

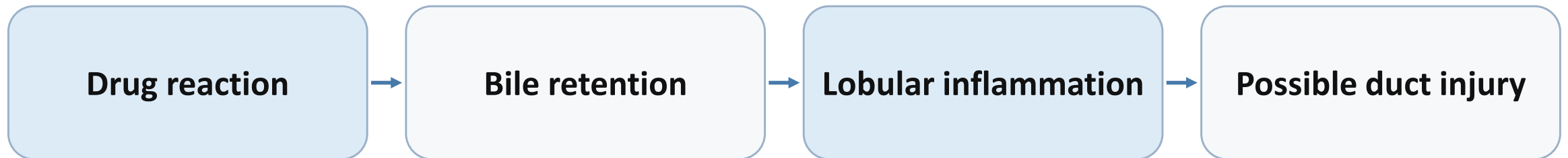
- Bile accumulates without a strong accompanying inflammatory infiltrate.
- Contraceptive and anabolic steroids, some antibiotics, and antiretroviral therapy as associations.
- The absence of florid hepatitis is central to the “bland” descriptor.



Schematic bile retention; Not a microscopic specimen.

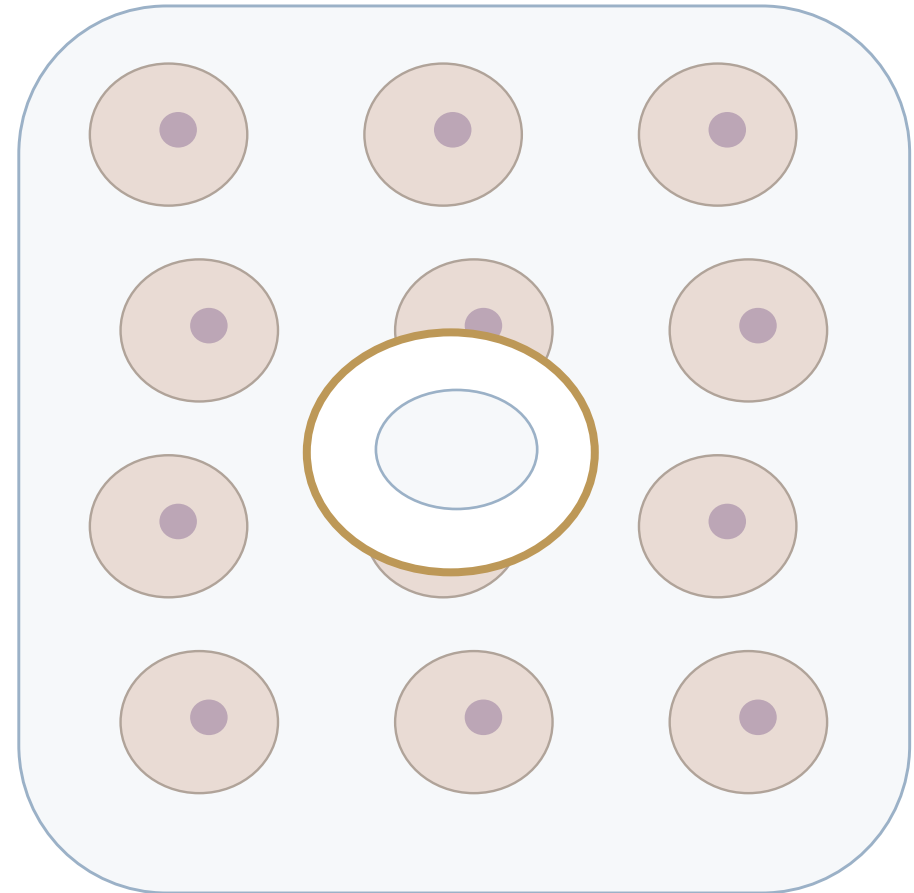
Cholestatic hepatitis combines two injury processes

- Cholestasis occurs together with lobular necroinflammatory activity.
- In some cases the bile ducts are damaged or destroyed.
- Textbook examples include antibiotics, phenothiazines, and statins.



Persistent cholestasis may reflect duct loss

- Some bile duct–centered reactions progress to chronic cholestasis.
- Ductular reaction may coexist with duct injury.
- A minority develop bile duct loss, making persistence possible after exposure ceases.



Schematic portal bile duct alteration.

Chronic hepatitis is a recognized drug pattern

Acute injury

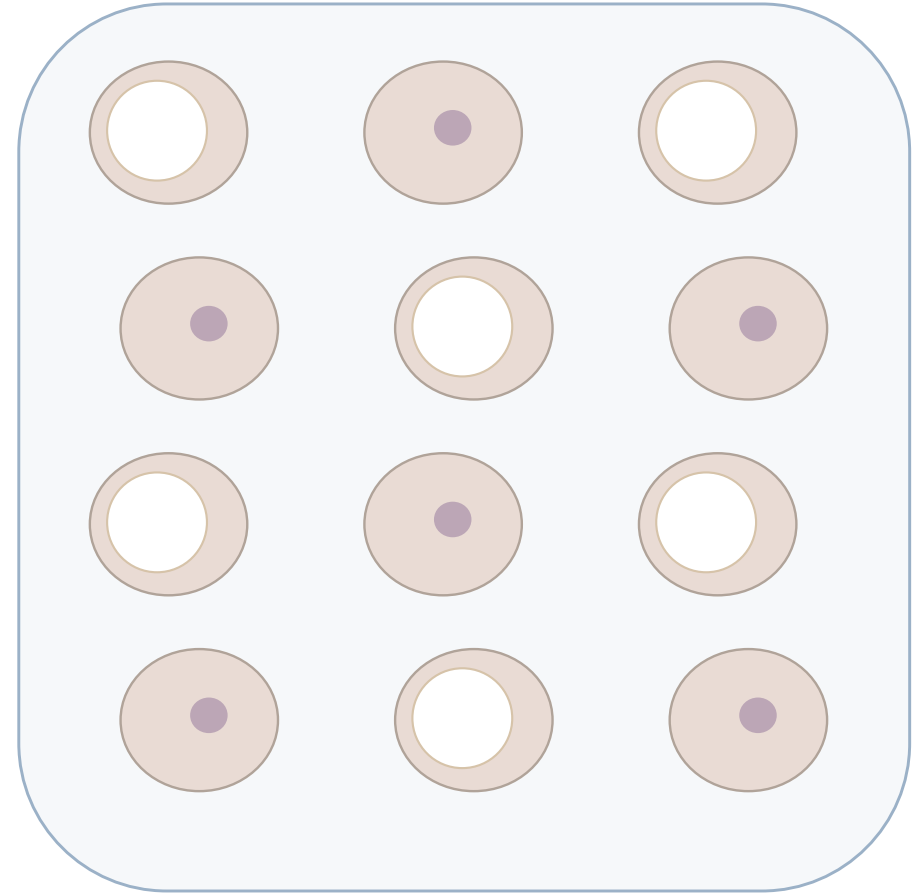
- Lobular activity
- Necrosis $\pm$ cholestasis
- Variable inflammation

Chronic injury

- Portal-based inflammation
- Progressive fibrosis possible
- May resemble chronic hepatitis

Some drugs produce a steatotic phenotype

- Large and small lipid droplets can appear within hepatocytes.
- Corticosteroids, methotrexate, and parenteral nutrition among associations.
- Drug-associated fatty change requires differentiation from other steatotic liver diseases.



Schematic hepatocellular fat accumulation.

Macrovesicular and microvesicular fat differ

Macrovesicular

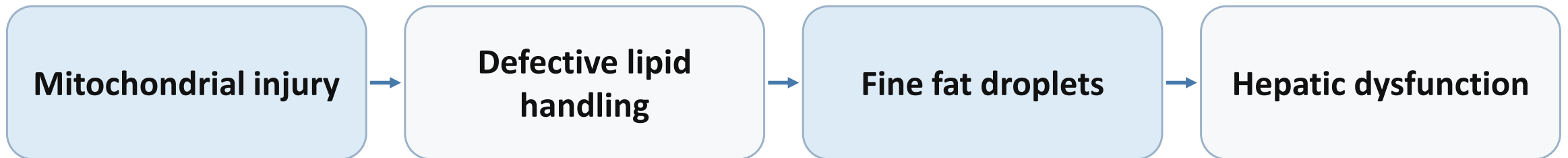
- Dominant large fat vacuole
- Nucleus often displaced
- Several metabolic and drug causes

Microvesicular

- Numerous small vacuoles
- Mitochondrial dysfunction implicated
- Valproate; Tetracycline; Others

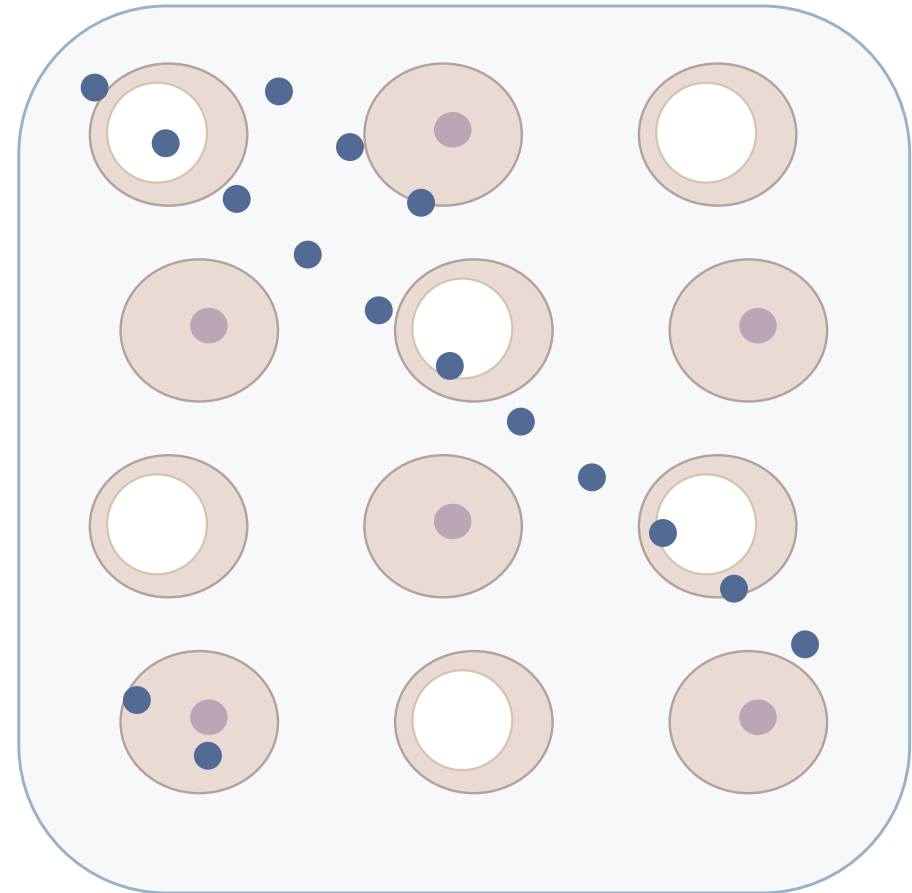
Microvesicular steatosis implicates mitochondria

- The textbook links this phenotype with mitochondrial dysfunction.
- Examples include tetracycline, valproic acid, and zidovudine.
- Diffuse mitochondrial failure can impair liver function even without massive necrosis.



Drug-related steatohepatitis is a separate phenotype

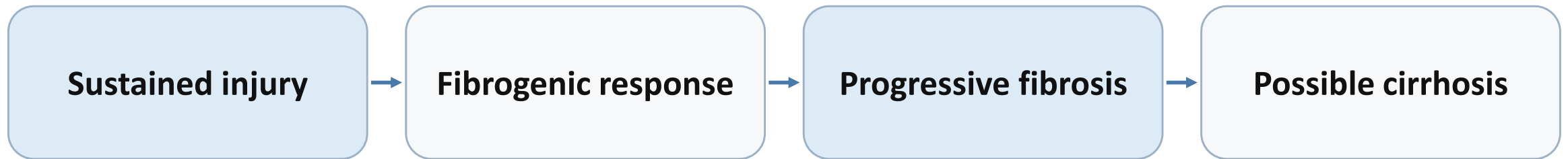
- Amiodarone, tamoxifen, irinotecan, and methotrexate may produce steatohepatitis-like injury.
- The table mentions steatohepatitis with Mallory hyaline for selected agents.
- Histologic overlap with metabolic and alcohol-associated steatohepatitis requires clinical context.



Conceptual combination of fat and inflammatory injury.

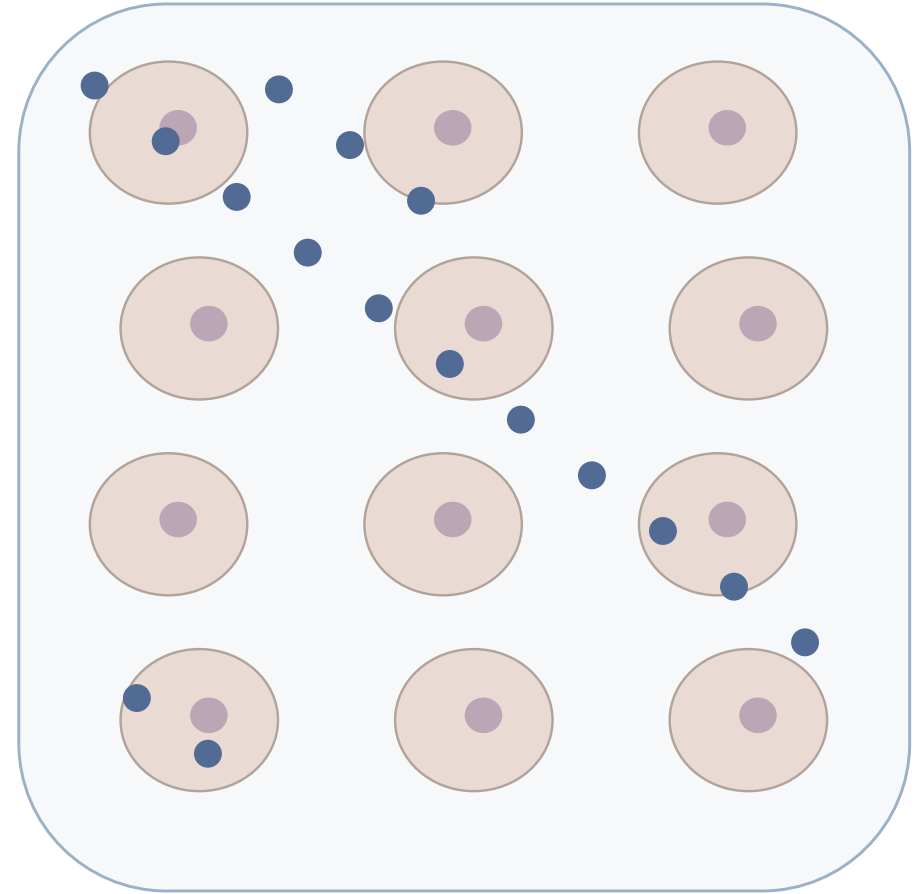
Long-term injury can culminate in fibrosis

- Periportal and pericellular fibrosis may develop in toxic or drug-associated injury.
- The source lists methotrexate, alcohol, enalapril, and retinoids among associations.
- Cirrhosis is possible, but not the typical outcome of every DILI episode.



Granulomatous reactions broaden the differential

- Noncaseating epithelioid granulomas may accompany drug reactions.
- Examples in the source include sulfonamides, amiodarone, and isoniazid.
- Allopurinol is associated with fibrin-ring granulomas in the source table.



Schematic granulomatous reaction.

Vascular injury may be the dominant lesion

- Toxins or drugs can damage sinusoidal or venous endothelium.
- The resulting pathology may involve obstruction, congestion, or blood-filled spaces.
- These changes are distinct from hepatocyte-centered hepatitis.

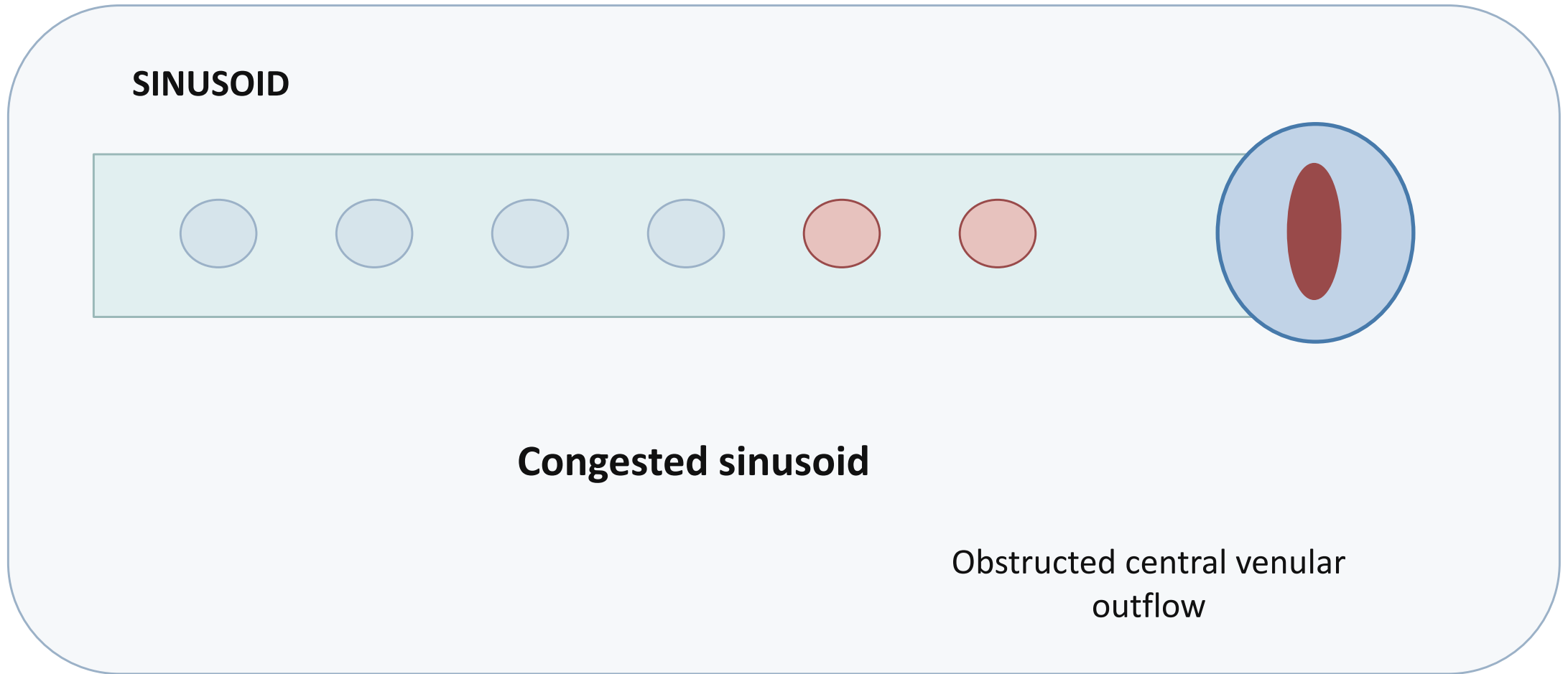
Sinusoidal obstruction

Budd–Chiari pattern

Peliosis hepatis

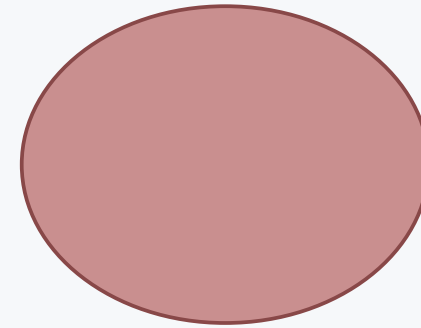
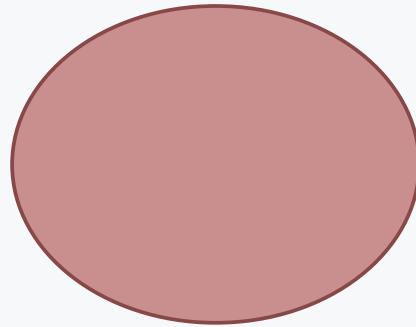
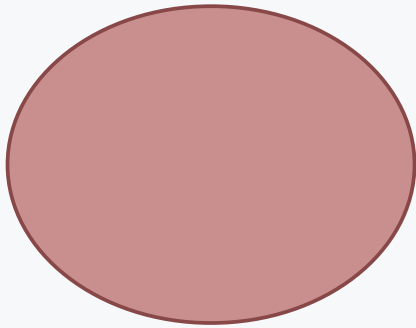
Vascular congestion

Sinusoidal obstruction syndrome



Original conceptual vascular schematic; Not clinical histology.

Peliosis hepatis features blood-filled cavities

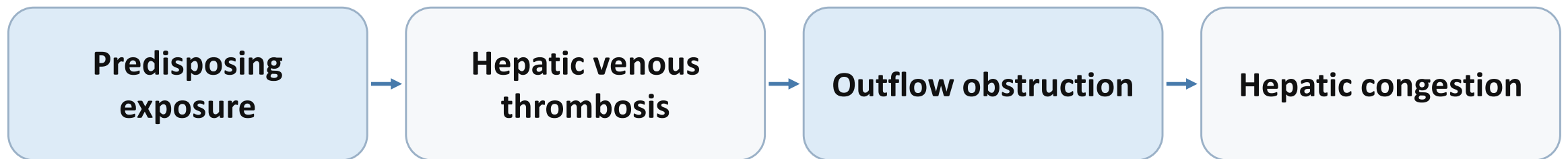


Blood-filled cavities within parenchyma

Original conceptual vascular schematic; Not clinical histology.

Budd–Chiari is an outflow-obstruction phenotype

- Hepatic venous outflow obstruction is a distinct vascular disorder.
- The table lists oral contraceptives as a relevant association.
- This association should not be mistaken for proof of causality in an individual patient.



Some exposures are linked to hepatic neoplasia

Neoplastic lesion	Associated agent
Hepatocellular adenoma	Oral contraceptives; Anabolic steroids
Hepatocellular carcinoma	Alcohol; Thorotrast
Cholangiocarcinoma	Thorotrast
Angiosarcoma	Thorotrast; Vinyl chloride

Patterns and representative associations

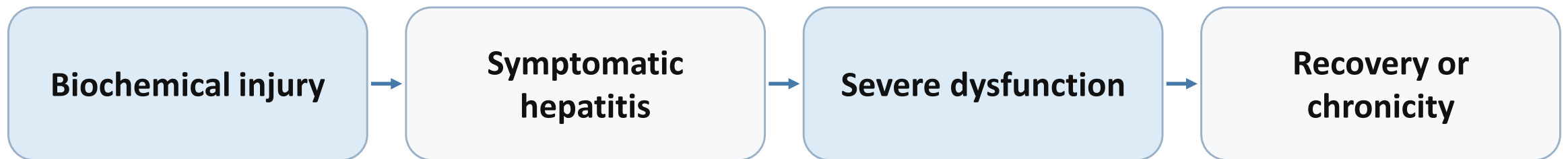
Pattern	Morphologic emphasis	Examples
Bland cholestasis	Bile without much inflammation	Anabolic steroids
Hepatitis	Inflammatory injury $\pm$ necrosis	Antimicrobials
Necrosis dominant	Confluent necrosis	Acetaminophen
Microvesicular fat	Numerous small fat droplets	Valproate; Tetracycline

Additional lesions and associated agents

Pattern	Diagnostic structure	Examples
Granulomatous	Epithelioid or fibrin-ring granulomas	Isoniazid; Allopurinol
Sinusoidal obstruction	Sinusoidal / venular injury	Oxaliplatin; Azathioprine
Peliosis	Blood-filled cavities	Anabolic steroids; Tamoxifen
Steatohepatitis	Fat with hepatocyte injury	Amiodarone; Irinotecan

Presentation ranges from silent injury to liver failure

- DILI may first be recognized as abnormal liver enzyme tests.
- Some patients develop jaundice or an acute hepatitis-like illness.
- Severe cases progress to failure; Others manifest prolonged cholestasis or chronic disease.



Biochemistry suggests pattern, not etiology

Laboratory pattern

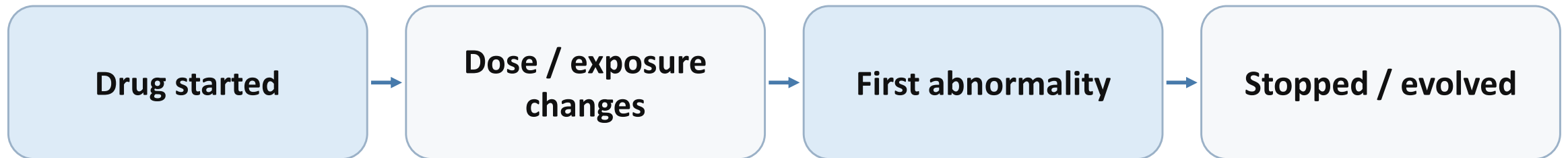
- ALT predominance
- ALP predominance
- Both increased

Interpretive limitation

- Pattern is not cause
- Histology may overlap
- Timing matters

A medication history should be chronological

- Document the date every potentially relevant agent was started.
- Record dose changes, combinations, interruptions, and withdrawal.
- Link the first laboratory or symptomatic abnormality to this exposure map.



Establish an alternative-cause differential

- Viral hepatitis and autoimmune hepatitis can produce similar inflammation.
- Steatotic liver disease can explain fatty change or steatohepatitis.
- Biliary and vascular disease may mimic cholestatic or venous patterns.

Viral infection

Autoimmune hepatitis

Steatotic disease

**Biliary / vascular
causes**

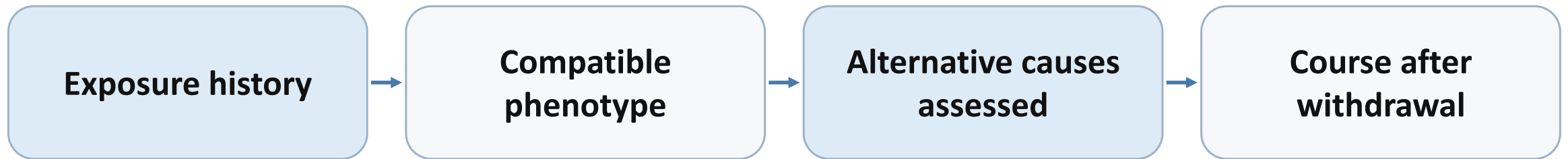
Biopsy is a pattern-recognition tool

- Hepatic tissue can show necrosis, portal/lobular activity, duct injury, fat, granulomas, or vascular injury.
- More than one pattern may coexist.
- The pathology report should express degree and distribution of injury without assuming causality.

Pathology supports an attribution; It rarely proves the responsible drug.

Improvement after withdrawal supports attribution

- A temporal relationship between exposure and onset is necessary for diagnosis.
- Excluding plausible alternative causes strengthens the assessment.
- Recovery after stopping the agent supports DILI in many cases, but not every injury resolves promptly.



An adverse drug reaction may mimic autoimmunity

Overlapping findings

- Plasma-cell inflammation
- Interface injury
- Autoantibodies may occur

Discriminating context

- Medication chronology
- Other autoimmune evidence
- Clinical course

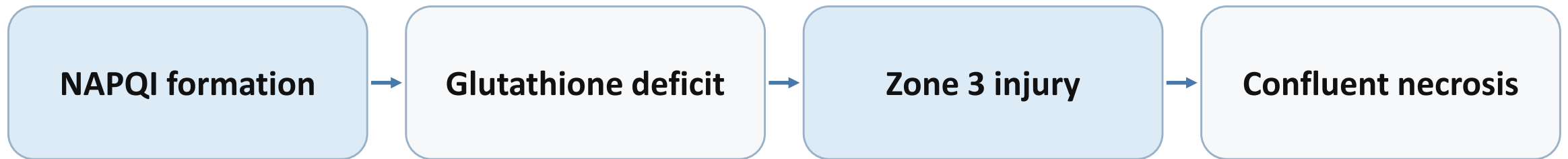
Teaching case: Marked necrosis after overdose

- Illustrative scenario: An adult presents after an excessive acetaminophen ingestion.
- The biopsy concept is zone 3 confluent necrosis with limited inflammation.
- Which mechanism most directly explains the zonal damage?

Discuss the morphologic mechanism and differential

Case interpretation: Intrinsic hepatotoxicity

- An exposure–response relationship is central to this case.
- Glutathione normally detoxifies NAPQI; Overdose overwhelms this defense.
- Centrilobular necrosis is compatible with metabolic activation of the toxin.



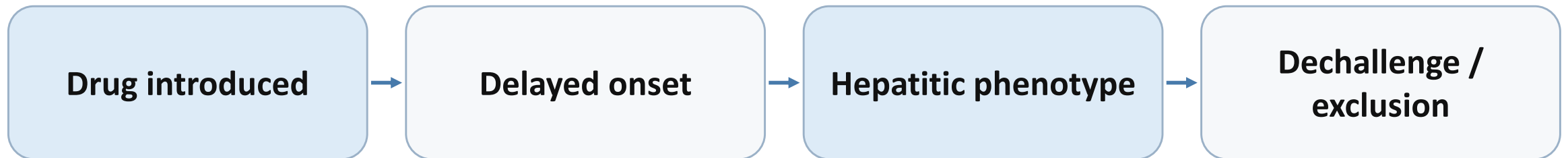
Teaching case: Antibiotic-associated hepatitis

- Illustrative scenario: Liver tests become abnormal weeks after a new antimicrobial.
- Liver biopsy shows lymphocytic lobular hepatitis with eosinophils and scattered cell death.
- Why is histology alone insufficient to confirm a drug reaction?

Discuss the morphologic mechanism and differential

Case interpretation: Idiosyncratic hepatitis

- The latency is compatible with an idiosyncratic reaction.
- An inflammatory infiltrate does not identify the responsible molecule.
- The diagnostic case strengthens when alternatives are excluded and injury improves after withdrawal.



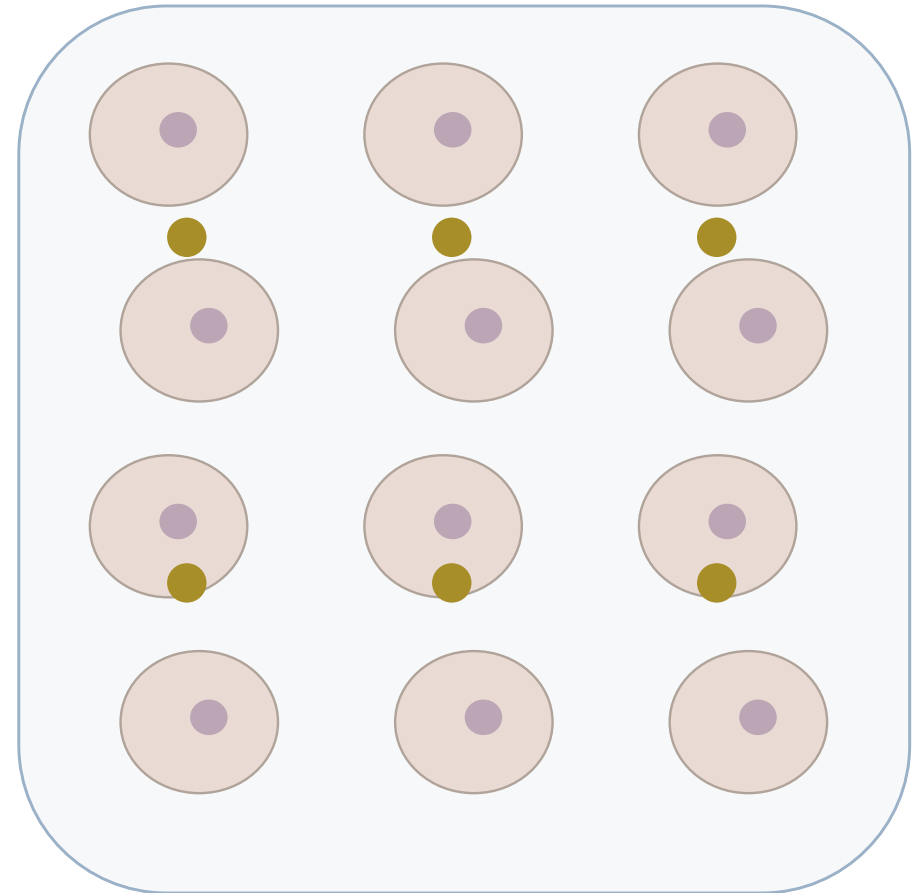
Teaching case: Cholestasis with little inflammation

- Illustrative scenario: Cholestatic liver tests follow an anabolic steroid exposure.
- Schematic biopsy pattern: Accumulated bile with little lobular inflammation.
- Which named pattern best captures this morphology?

Discuss the morphologic mechanism and differential

Case interpretation: Bland cholestasis

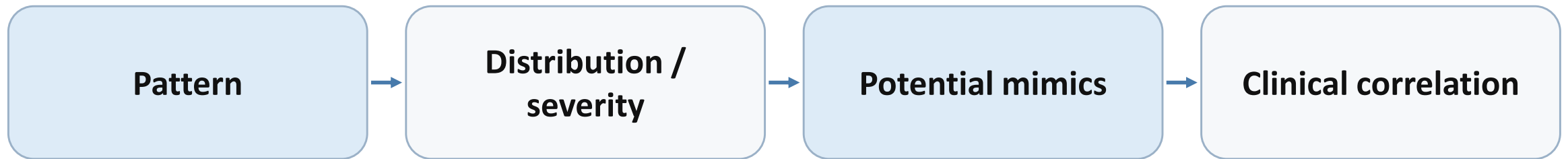
- The pattern is defined by bile retention with minimal inflammatory activity.
- Steroid-associated cholestasis is included among the source examples.
- Other cholestatic causes still require clinical exclusion.



Schematic; No actual histopathology supplied.

A structured final pathology synthesis

- State the predominant pattern: Hepatitic, cholestatic, mixed, or another recognizable lesion.
- Describe severity, distribution, bile duct abnormalities, fat, vascular injury, and fibrosis as applicable.
- Correlate the findings with drug exposure and the broader clinical work-up.



High-yield distinctions

- Predictable intrinsic injury is exemplified by acetaminophen and necrosis-dominant pathology.
- Idiosyncratic injury frequently resembles acute hepatitis and may follow a delayed onset.
- Steatotic, cholestatic, vascular, granulomatous, and neoplastic lesions also belong in the spectrum.
- Diagnosis rests on chronology, competing-cause exclusion, and follow-up.

References and suggested reading

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Elsevier; 2026.
- Drug- and Toxin-Induced Liver Injury: pathogenesis, morphologic patterns, and clinical features.
- Acetaminophen: hepatic metabolism, reactive intermediates, and glutathione-dependent detoxification.