
Cholelithiasis (Gallstones)

Pathogenesis • Morphology • Clinicopathologic correlations

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Learning outcomes

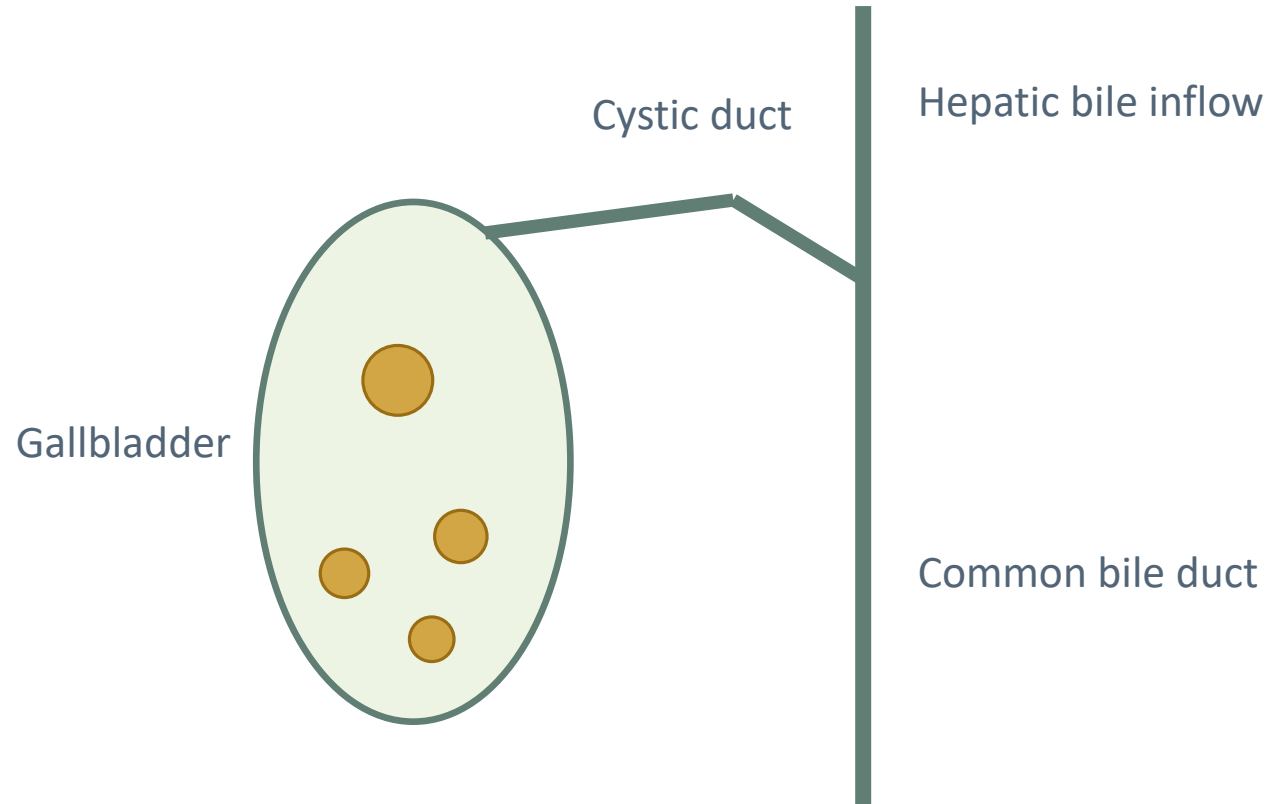
- Distinguish cholesterol stones from pigment stones by composition and context.
- Explain the four interacting mechanisms of cholesterol stone formation.
- Relate bilirubin metabolism and infection to pigment stone formation.
- Predict complications from stone size and anatomic location.

The burden of cholelithiasis

- More than 95% of biliary tract disease is attributable to gallstones.
- Gallstones affect 10%–20% of adults in high-resource countries.
- Despite their frequency, most stones remain clinically silent.

Prevalence is not equivalent to symptomatic disease.

Anatomic sites determine consequences



Cystic duct obstruction can produce gallbladder outlet pain.

Migration into the common duct can cause downstream complications.

Bile is stored and concentrated in the gallbladder

- The liver may secrete up to 1 L of bile daily.
- Between meals, the gallbladder stores and concentrates bile.
- Adult gallbladder capacity is approximately 50 mL.
- Gallbladder removal does not ordinarily cause fat malabsorption.

Two principal classes of gallstones

Cholesterol stones

- More than 50% crystalline cholesterol monohydrate
- Higher prevalence in the United States and western Europe
- Cholesterol supersaturation and nucleation

Pigment stones

- Predominantly calcium salts of bilirubin
- Predisposition from hemolysis or biliary infection
- Black and brown subtypes differ in setting

Classification: Composition at a glance

Cholesterol stones	Pigment stones
>50% cholesterol monohydrate	Predominantly calcium bilirubinate
Gallbladder origin	Black: gallbladder; brown: infected large ducts
Pale yellow in pure form	Black or brown; different textures

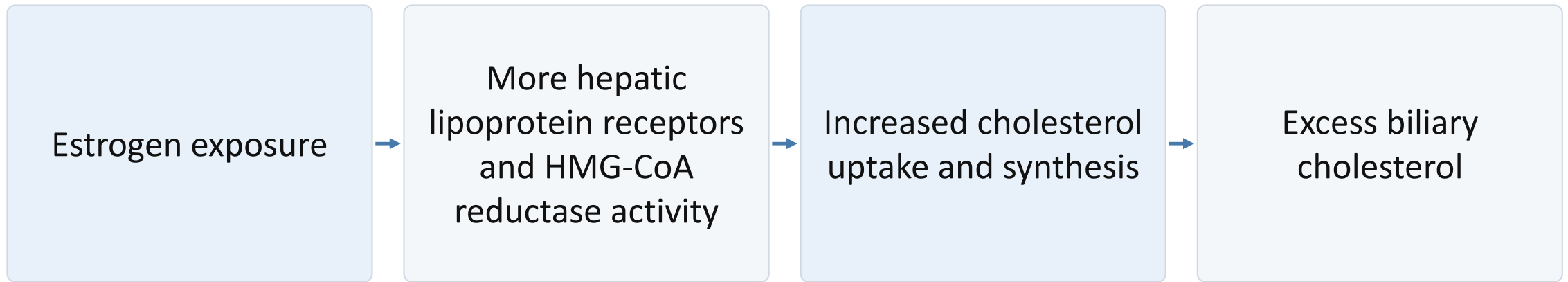
Geographic distribution differs by stone type

- Cholesterol stones account for about 90% of gallstones in the United States and western Europe.
- Their frequency is lower in low-resource countries.
- Certain Native American groups have exceptionally high prevalence.
- Pigment stones are particularly linked to hemolytic and biliary infectious settings.

Age and sex influence cholesterol stones

- Prevalence rises throughout adult life.
- Most affected patients are middle-aged or older.
- Female sex is associated with greater prevalence.
- Increased biliary cholesterol secretion helps explain these associations.

Estrogen exposure enhances cholesterol secretion



Pregnancy and oral contraceptive exposure are listed risk factors.

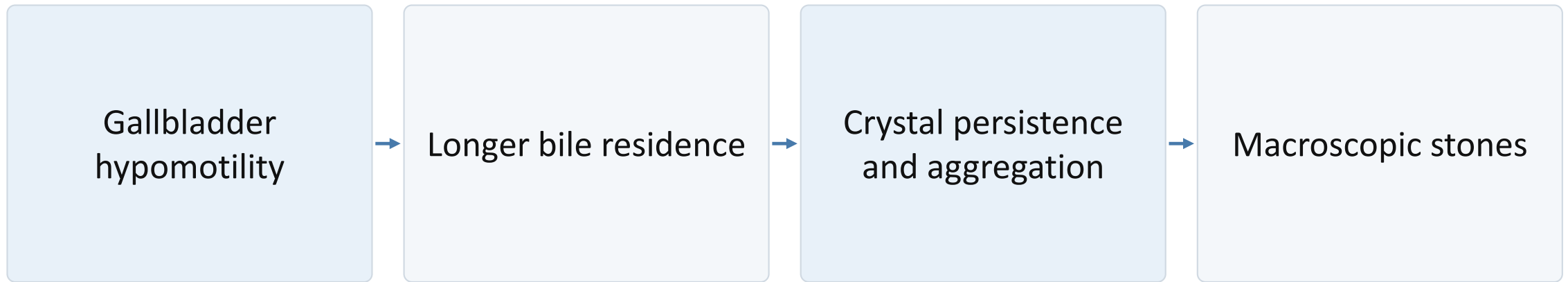
Obesity and metabolic syndrome

- Both are strongly associated with cholesterol gallstones.
- The source links obesity to increased biliary cholesterol secretion.
- Metabolic risk and lithogenic bile are mechanistically connected.
- Population risk factors do not establish stone composition in an individual.

Rapid weight reduction is a gallstone risk

- Rapid weight loss is associated with increased biliary cholesterol secretion.
- The resulting altered cholesterol balance favors supersaturation.
- This risk differs from chronic obesity but converges on lithogenic bile.

Gallbladder stasis promotes crystallization



Neurogenic or hormonal stasis can predispose to both stone classes.

An inherited component: ABCG8

- ABCG8 encodes a sterol transporter in hepatocytes.
- A common ABCG8 variant is associated with increased cholesterol stone risk.
- The relevant transporter family comprises ATP-binding cassette proteins.
- Genetic susceptibility acts alongside acquired and environmental risks.

Additional cholesterol-stone predispositions

- Inborn disorders of bile acid metabolism.
- Hyperlipidemia syndromes.
- Gallbladder stasis and female sex hormone exposure.
- Geographic and ancestral variation in baseline risk.

Risk factor map: Cholesterol versus pigment

Cholesterol stones	Pigment stones
Age, estrogen, female sex	Chronic hemolytic anemia
Obesity; metabolic syndrome	Biliary infection / infestation
Rapid weight reduction	Ileal disease; resection or bypass
Gallbladder stasis	Cystic fibrosis with pancreatic insufficiency

Hemolysis predisposes to pigment stones

- Chronic red-cell destruction increases bilirubin delivery to the liver.
- More bilirubin glucuronides are secreted into bile.
- Deconjugation can generate sufficient unconjugated bilirubin to precipitate.
- Black stones classically form in a sterile gallbladder environment.

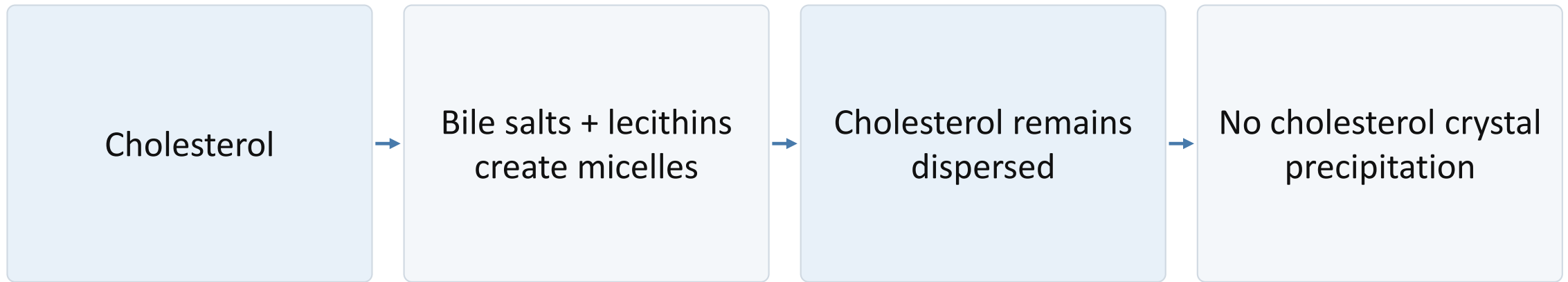
Biliary infection predisposes to pigment stones

- Microorganisms may produce β -glucuronidase.
- The enzyme hydrolyzes bilirubin glucuronides to unconjugated bilirubin.
- The resulting poorly soluble bilirubin calcium salts favor stone formation.
- Brown stones typically arise in infected large bile ducts.

Ileal disease and altered intestinal physiology

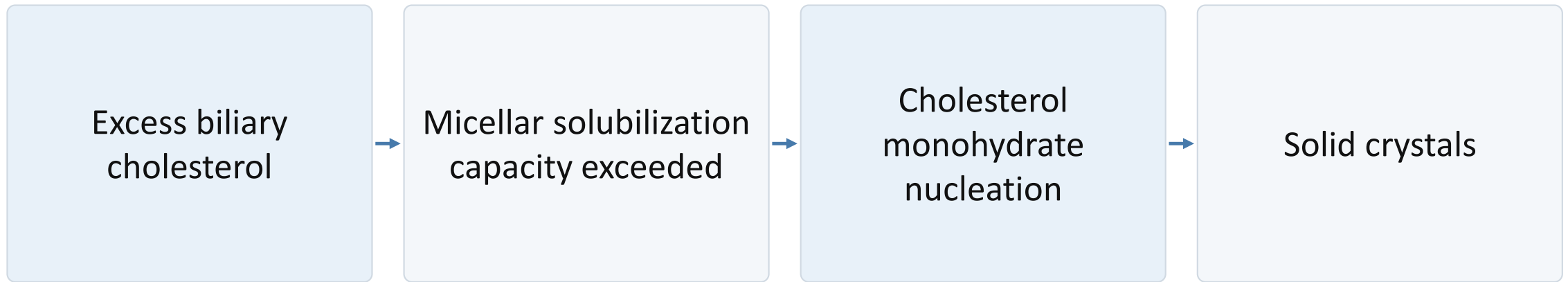
- Severe ileal dysfunction or bypass is associated with pigment stones.
- Ileal Crohn disease, resection and bypass appear among Robbins risk factors.
- Cystic fibrosis with pancreatic insufficiency also features in this group.
- The textbook groups these settings as predispositions; The exact individual pathway varies.

Cholesterol in bile: Soluble versus insoluble



Stone formation requires that cholesterol exceed bile's solubilizing capacity.

Supersaturation shifts cholesterol into crystals

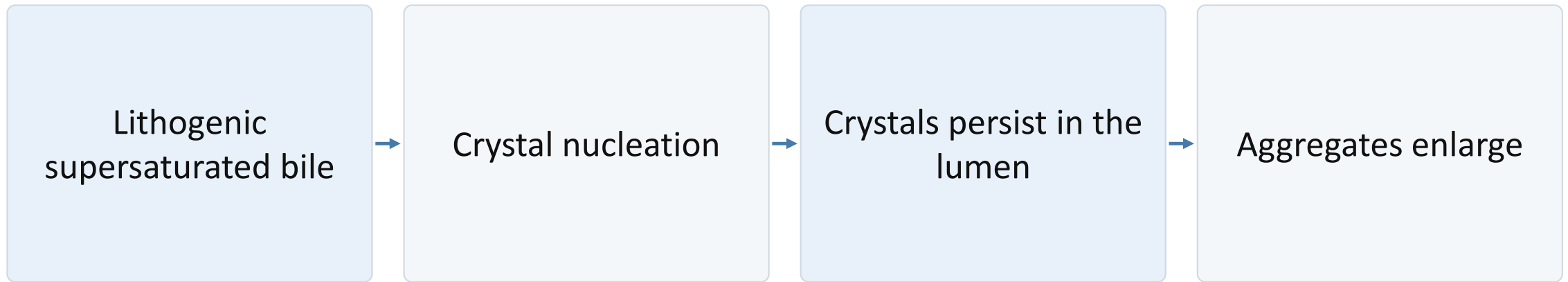


Supersaturation is a critical starting condition—not sufficient by itself.

Four contributors to cholesterol stone formation

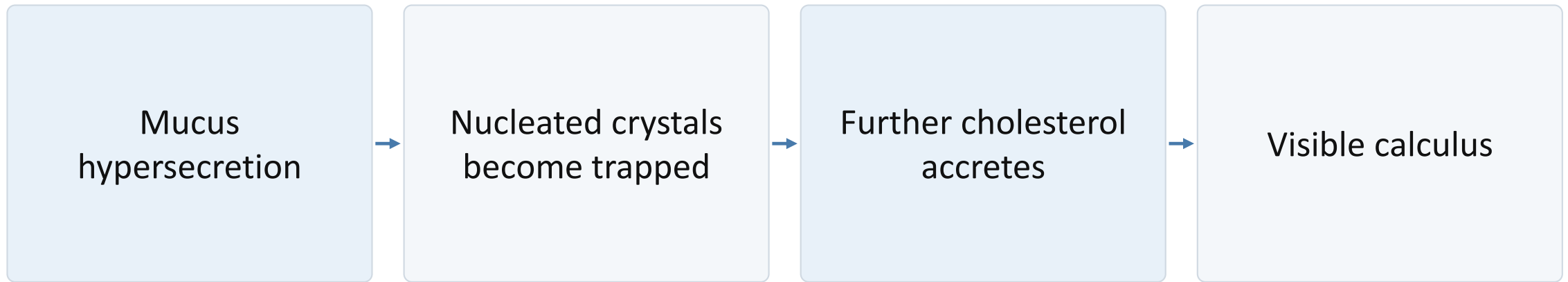
- Bile supersaturation with cholesterol.
- Hypomotility of the gallbladder.
- Accelerated cholesterol crystal nucleation.
- Gallbladder mucus hypersecretion and crystal trapping.

Accelerated nucleation is a distinct step



Supersaturation and nucleation are related, but not identical.

Mucin retains crystals and enables growth

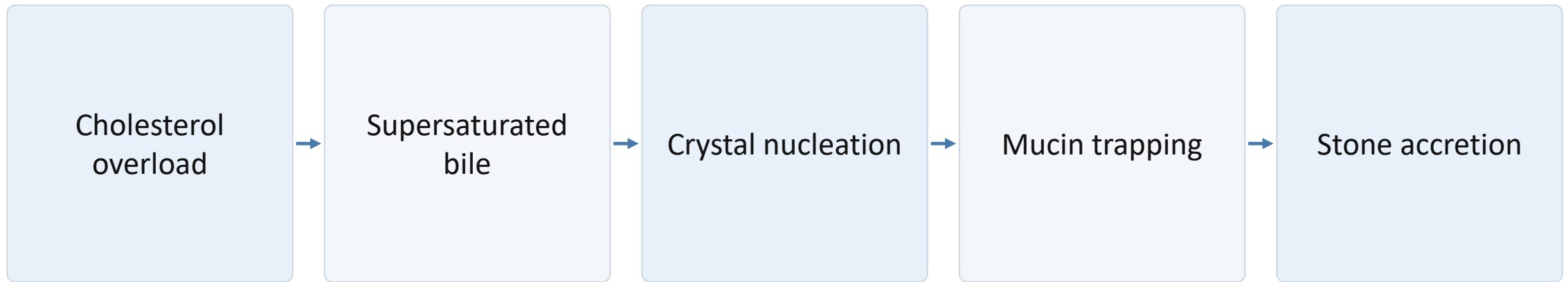


Mucin glycoproteins also provide structural scaffolding to all stone types.

Why gallbladder hypomotility matters

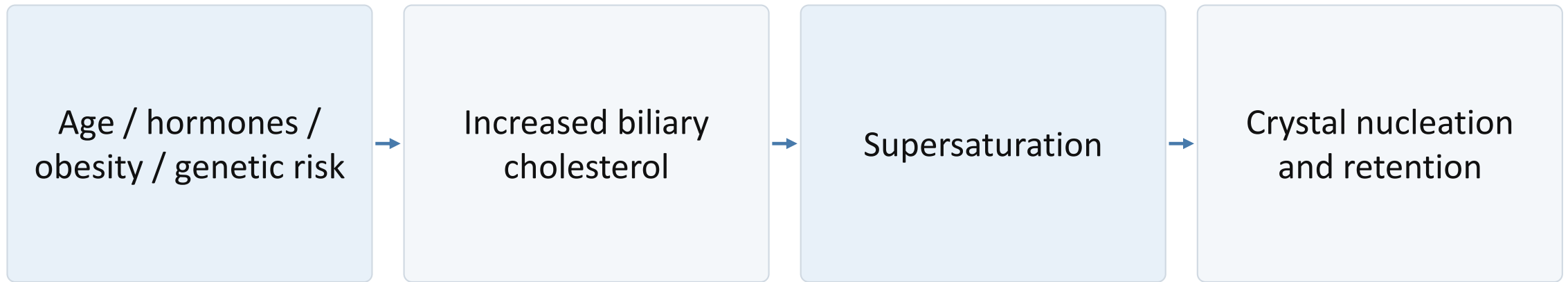
- Effective gallbladder emptying helps clear crystalline material.
- Stasis creates a favorable environment for nucleation and retention.
- Hormonal and neurogenic factors may contribute to hypomotility.
- Stasis predisposes to both cholesterol and pigment stones.

Pathogenesis in one integrated sequence



Reduced motility favors persistence through the sequence.

Epidemiologic risks converge on bile chemistry

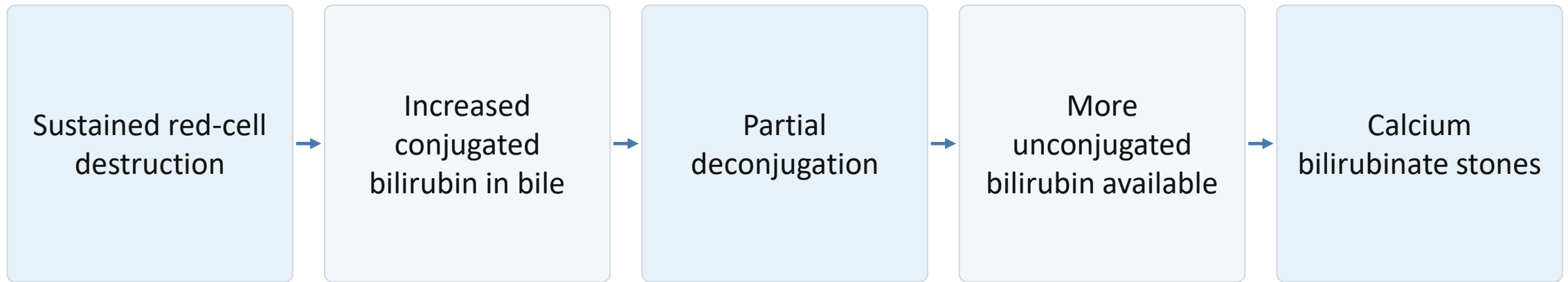


Different exposures may act through the same proximal physicochemical step.

Pigment stone chemistry

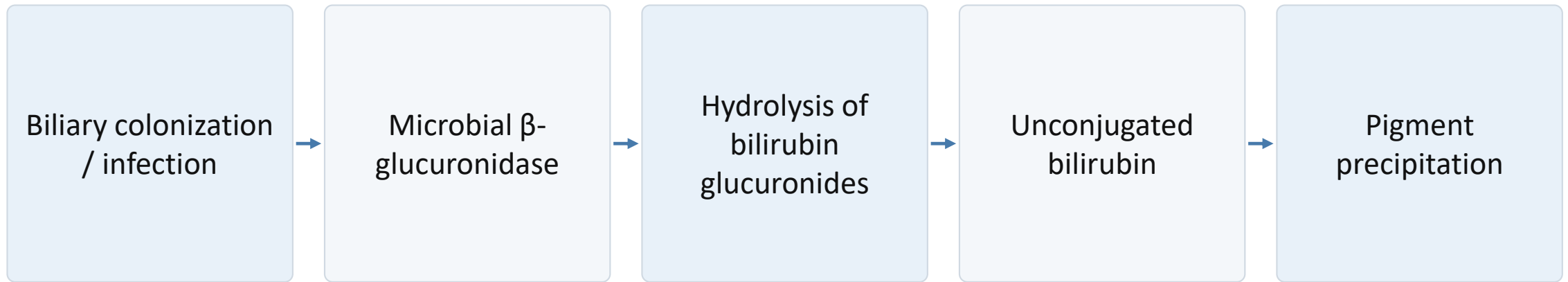
- Pigment stones contain insoluble calcium salts of unconjugated bilirubin.
- Inorganic calcium salts and mucin are additional constituents.
- Black and brown stones differ in associated setting and constituents.
- Conjugated and unconjugated bilirubin must be distinguished mechanistically.

Chronic hemolysis drives pigment formation



About 1% of biliary bilirubin glucuronides are deconjugated.

Infected bile: Microbial β -glucuronidase



Organisms linked to pigment lithogenesis

- *Escherichia coli* and its microbial β -glucuronidase activity.
- *Ascaris lumbricoides* infestation.
- *Clonorchis sinensis* infestation.
- The source describes these infections as increasing pigment-stone likelihood.

The ileum is a pigment-stone risk context

- Severe ileal dysfunction or surgical bypass is associated with pigment stones.
- Crohn disease affecting the ileum is explicitly included.
- Biliary composition may become favorable to pigment precipitation.
- Do not infer that every patient with ileal disease will develop stones.

Black and brown pigment stones form in different settings

Black pigment stones	Brown pigment stones
Typically sterile gallbladder bile	Typically infected large bile ducts
Often associated with chronic hemolysis	Associated with microbial contamination
Oxidized calcium bilirubinate polymers	Includes calcium salts of fatty acids
Often hard/friable, irregular	Often soft, laminated, greasy

Black pigment stones: Major constituents

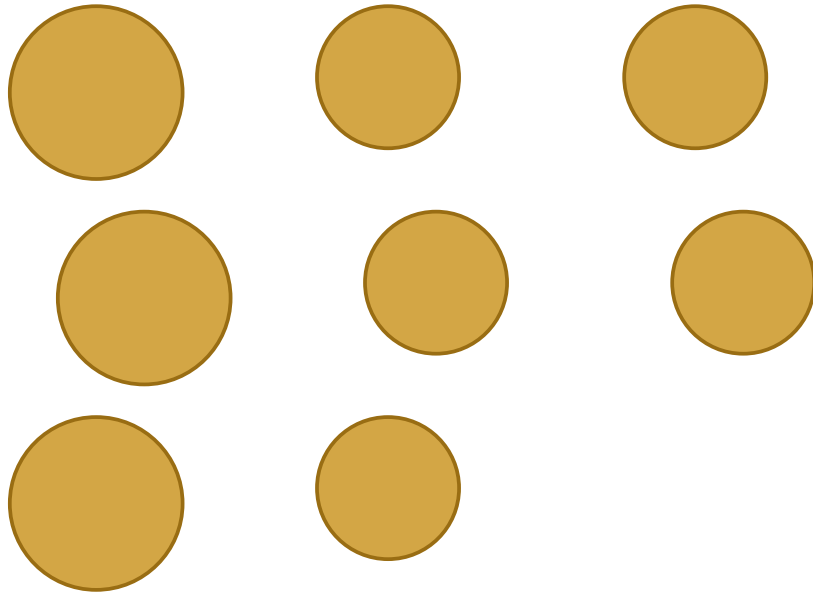
- Oxidized polymers of calcium salts of unconjugated bilirubin.
- Small amounts of calcium carbonate and calcium phosphate.
- Mucin glycoprotein and some cholesterol monohydrate crystals.
- Composition helps explain frequent radiopacity.

Brown pigment stones: Major constituents

- Bilirubin compounds similar to those in black stones.
- Additional cholesterol may be present.
- Calcium palmitate and calcium stearate are characteristic constituents.
- Calcium soaps accompany a soft, sometimes greasy texture.

Cholesterol stones: Characteristic gross appearance

ORIGINAL SCHEMATIC — NOT A GROSS SPECIMEN

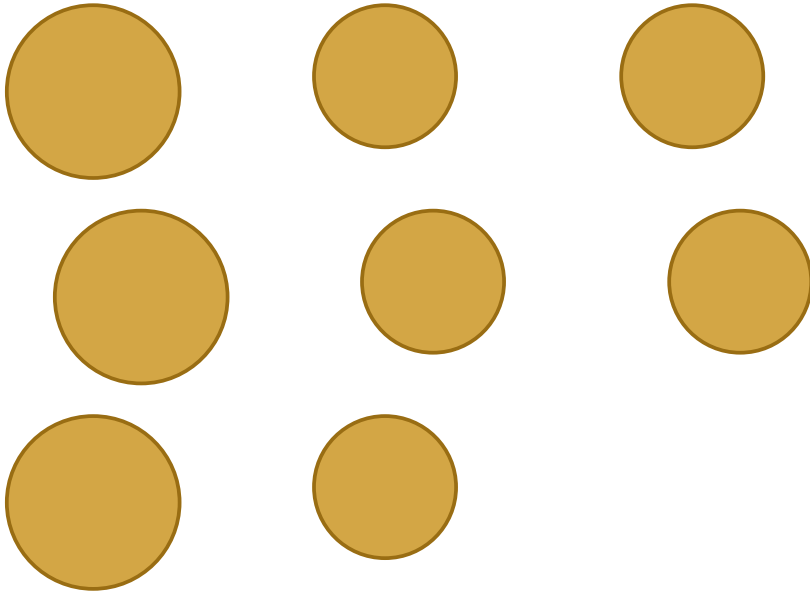


Pure cholesterol stones

- Pale yellow; Round to ovoid
- Hard, finely granular outer surface
- May be solitary or multiple
- Diameter may reach several centimeters

Multiple stones can become faceted

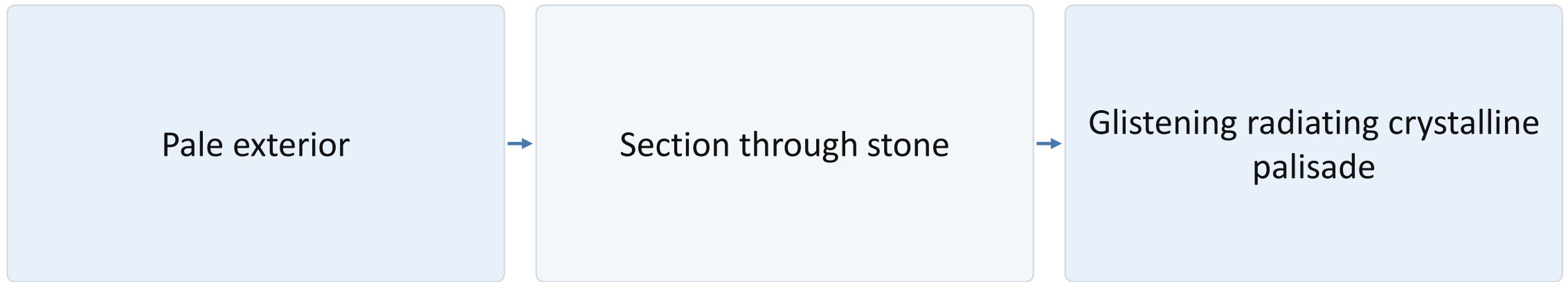
ORIGINAL SCHEMATIC — NOT A GROSS SPECIMEN



Shape reflects packing

- Closely apposed stones may flatten each other
- Facets reflect contact surfaces
- Rounded forms also occur
- Shape alone does not determine composition

Cut surface of a pure cholesterol stone



This text-based schematic captures the source description; No specimen micrograph is implied.

Mixed composition changes cholesterol-stone color

- Pure cholesterol stones are typically yellow.
- Increasing calcium salts and bilirubin can shift color to gray-white or black.
- Mixed stones may be laminated.
- Gross color is a clue, not an absolute chemical assay.

Radiographic visibility of cholesterol stones

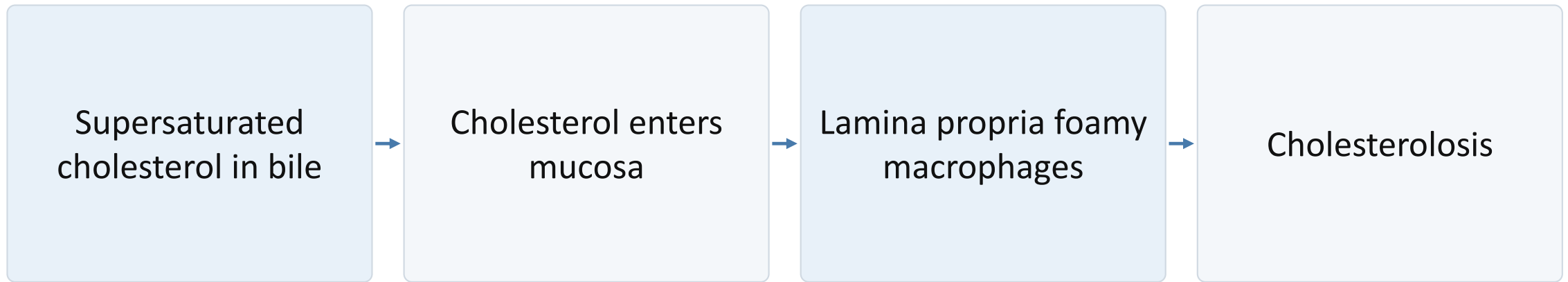
- Stones composed largely of cholesterol are generally radiolucent.
- Calcium carbonate renders about 10%–20% of cholesterol stones radiopaque.
- Radiopacity therefore reflects mineral content, not merely the category name.

Radiolucent $\neq$ absent; The term concerns plain-film x-ray attenuation.

Cholesterolosis links bile chemistry to mucosa

- Cholesterol from supersaturated bile can enter the gallbladder mucosa.
- The lamina propria may be distended by foamy macrophages.
- Cholesterolosis is a mucosal finding, not a subtype of gallstone.
- Gallstones and cholesterolosis can reflect a shared cholesterol-rich biliary milieu.

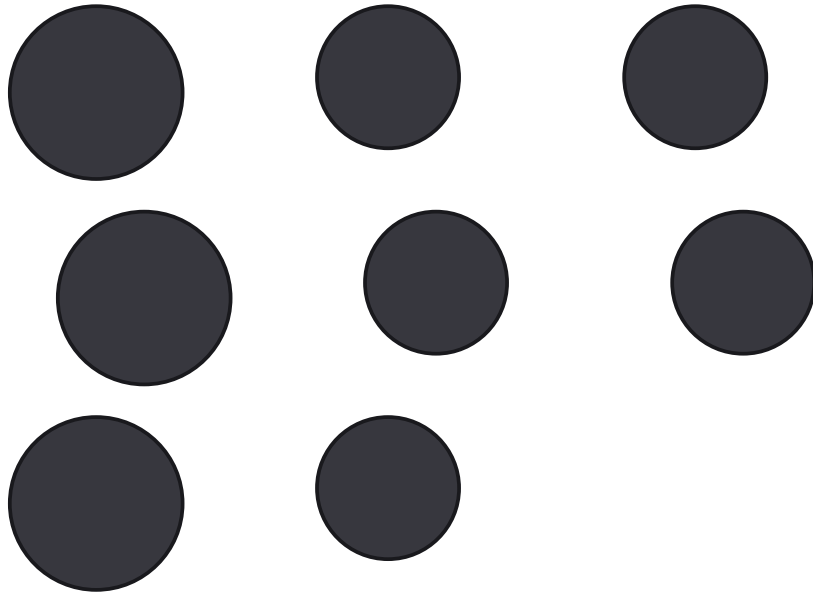
Cholesterolosis: A microscopic correlation



Histologic appearance comes from the Robbins figure caption; No genuine H&E was available for embedding.

Black pigment stones: Gross morphology

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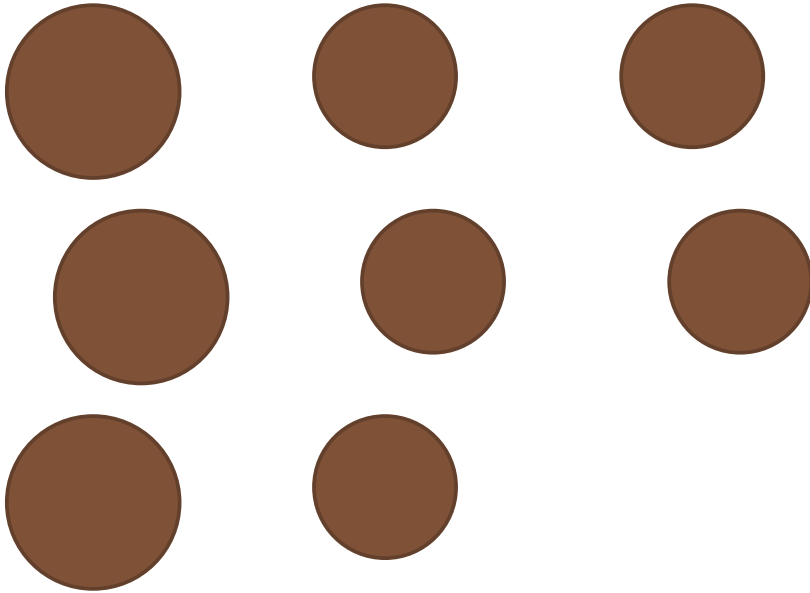


Black stones

- Usually numerous and small
- Rarely exceed 1.5 cm
- Friable with spiculated or molded contours
- Number inversely relates to stone size

Brown pigment stones: Gross morphology

ORIGINAL SCHEMATIC — NOT A GROSS SPECIMEN



Brown stones

- Brown coloration
- Often laminated and soft
- May feel greasy or soap-like
- Typically in infected large bile ducts

Radiopacity differs across pigment stones

Black pigment stones	Brown pigment stones
50%–75% radiopaque	Usually radiolucent
Calcium salts promote x-ray attenuation	Calcium soaps do not usually produce opacity
Opacity is a compositional feature	Location and infection provide context

Mucin is shared infrastructure in all stones

- Mucin glycoproteins form a scaffold in gallstone matrices.
- They also provide interparticle cement.
- This matrix supports cohesion as deposits accumulate.
- The same material plays a trapping role in cholesterol stone formation.

Morphology: Integrated comparison

Cholesterol	Black pigment	Brown pigment
Pale yellow when pure	Black	Brown
Hard; granular exterior	Friable; spiculated	Soft; laminated
Radiolucent unless calcified	Often radiopaque	Usually radiolucent
Gallbladder	Sterile gallbladder	Infected large ducts

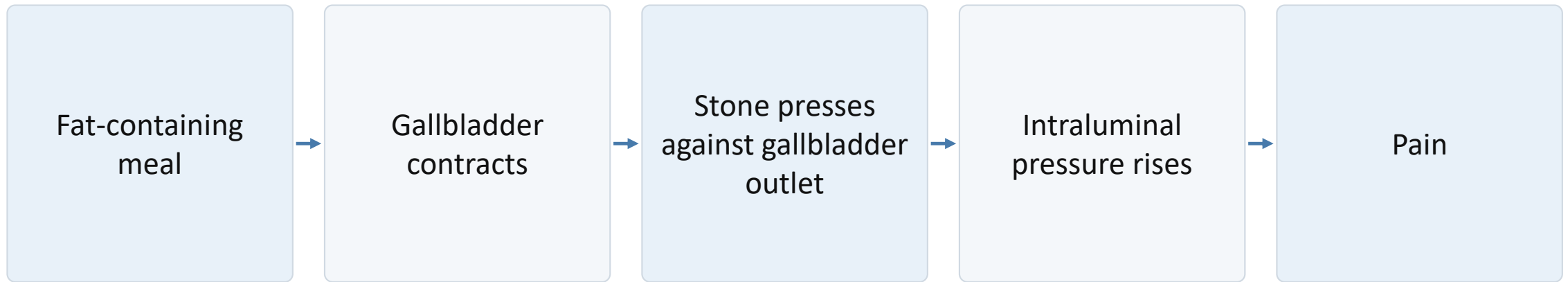
Most gallstones remain asymptomatic

- Stones can remain silent for decades.
- 70%–80% of affected individuals remain asymptomatic over their lifetime.
- Stone detection and symptomatic stone disease are clinically different states.

Transition from silent to symptomatic disease

- Asymptomatic patients may develop symptoms at rates up to approximately 4% per year on average.
- The risk of becoming symptomatic diminishes with time.
- These are natural-history estimates, not an individual prediction.

Biliary pain: An obstructive mechanism



“Biliary colic” is often a misnomer

- The reported pain can be severe or excruciating.
- Despite the name, it is usually constant rather than truly colicky.
- Gallbladder outlet obstruction during contraction is a key mechanism.
- Coexistent cholecystitis can independently contribute pain.

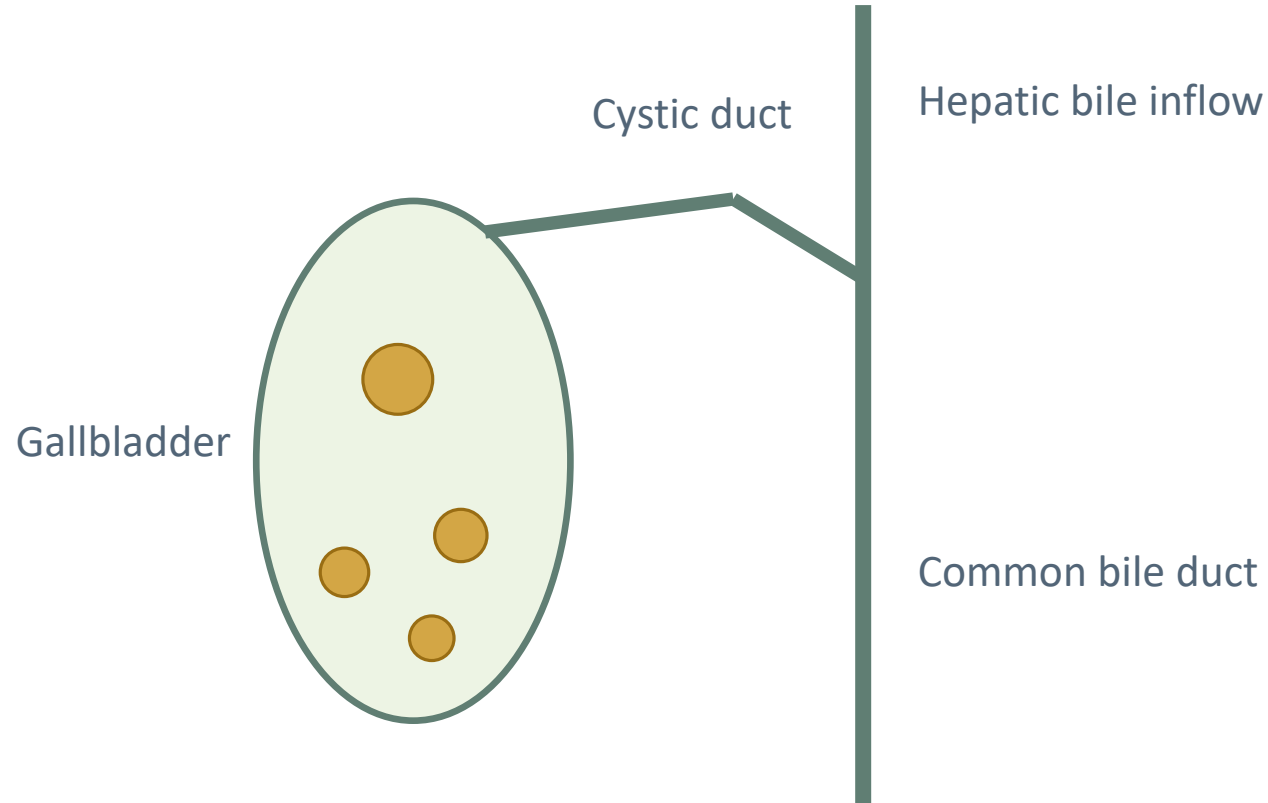
Anatomic distribution of biliary pain

- Pain typically localizes to the right upper quadrant or epigastrium.
- It may radiate to the right shoulder or back.
- Radiation does not by itself establish which duct contains a stone.
- Mechanistic context is important when interpreting symptoms.

Why small stones can be more dangerous

- Large stones are less likely to pass into the cystic or common bile duct.
- Small stones (“gravel”) are more likely to migrate into narrow ducts.
- Duct entry and obstruction drive several serious complications.
- Stone count and maximum diameter do not determine risk in isolation.

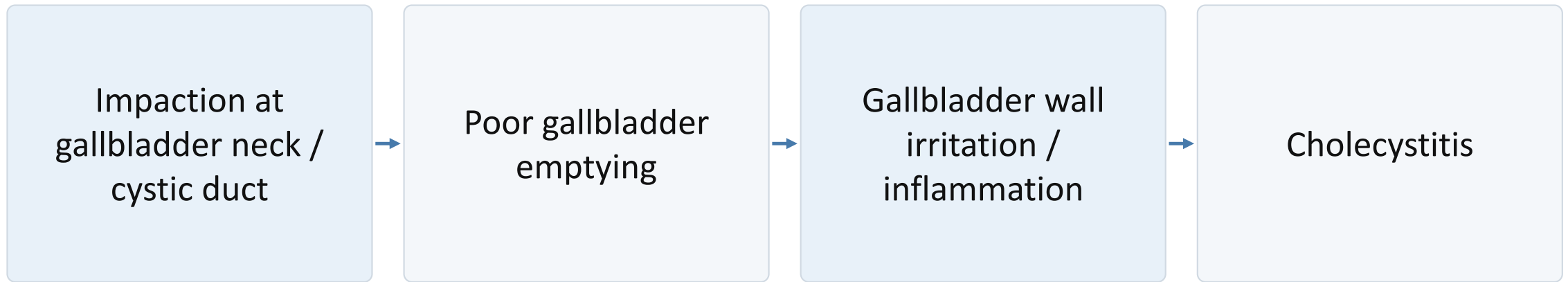
Stone location predicts the major complication



Cystic duct obstruction can produce gallbladder outlet pain.

Migration into the common duct can cause downstream complications.

Gallstone disease can progress to cholecystitis

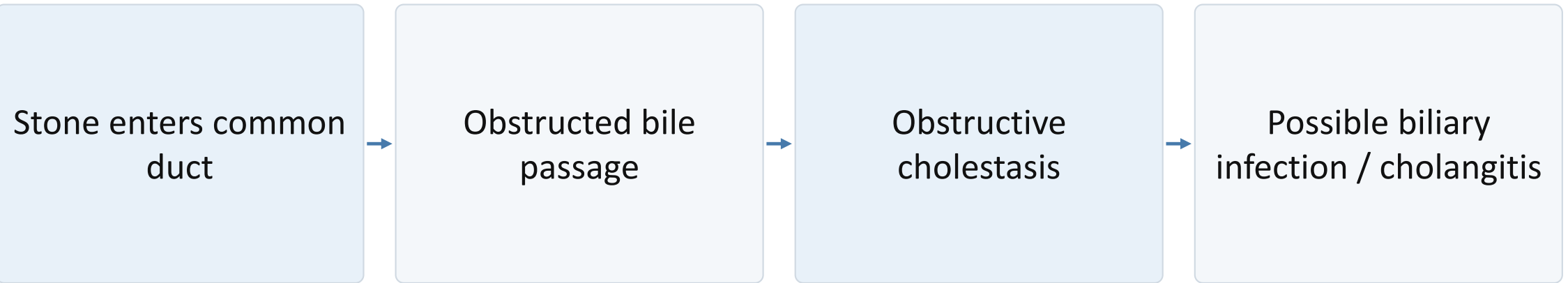


The neighboring Robbins section identifies stones as the usual setting for cholecystitis.

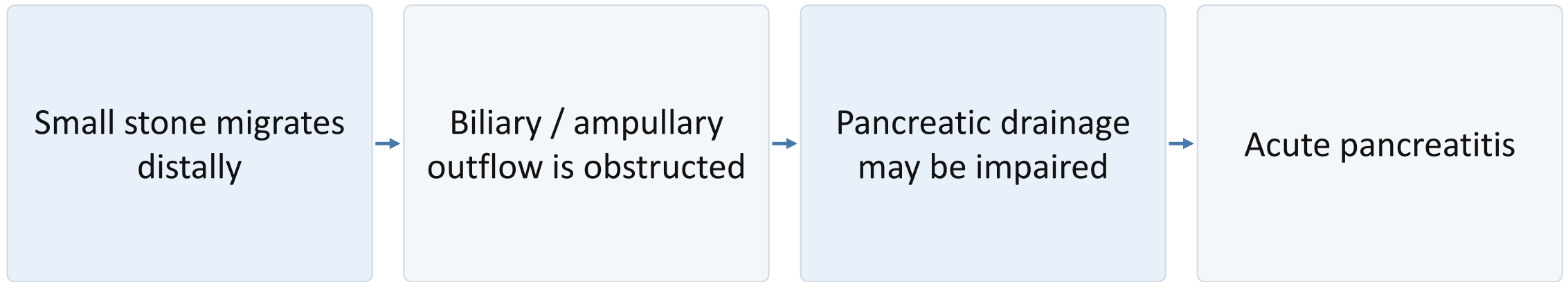
Severe local gallbladder complications

- Empyema: Purulent gallbladder complication.
- Perforation: Breach of the gallbladder wall.
- Fistula: Abnormal communication with a neighboring structure.
- All are recognized severe consequences of gallstone disease.

Common duct disease affects bile flow

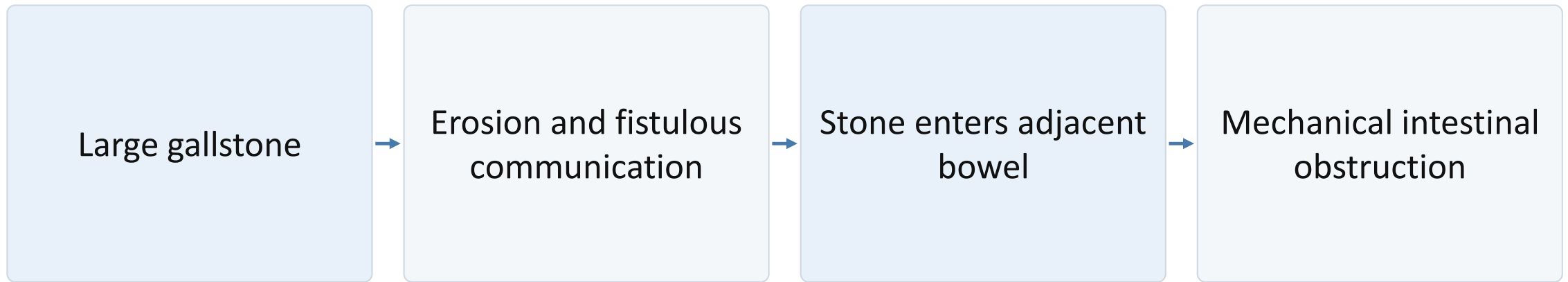


Gallstones are a trigger for pancreatitis



Pancreatitis is an identified complication; This is a simplified anatomical mechanism.

Large gallstones can obstruct bowel



Gallstone ileus; Robbins also mentions Bouveret syndrome in this context.

Gallstones and gallbladder carcinoma

- Gallstone disease is associated with increased gallbladder carcinoma risk.
- An association should not be interpreted as inevitable malignant transformation.
- The broader gallbladder carcinoma discussion belongs to its own topic.

Clinical location–consequence map

Stone location / event	Expected consequence
Gallbladder outlet impaction	Typical biliary pain
Gallbladder inflammation	Cholecystitis; may become complicated
Biliary duct obstruction	Cholestasis; possible cholangitis
Distal outflow obstruction	Possible pancreatitis
Large stone entering bowel	Gallstone ileus

Case application: Lithogenic bile

An adult with obesity and estrogen exposure has multiple pale yellow gallbladder calculi. The stones appear rounded and hard.

Interpret the clinicopathologic clues:

- Which compositional category is most likely?
- What is the proximal physicochemical abnormality?
- Name two additional mechanisms required for persistent stone growth.

Case application: Chronic hemolysis

A patient with a mechanical heart valve and chronic intravascular hemolysis has many small black gallstones.

Interpret the clinicopathologic clues:

- Which bilirubin pathway explains stone formation?
- Why is the appearance more consistent with black than brown pigment stones?

Case application: Dangerous gravel

An individual with known gallstones develops severe epigastric pain after a small calculus migrates out of the gallbladder.

Interpret the clinicopathologic clues:

- Why may a small calculus have greater obstructive potential than a large one?
- Which downstream complications must be recognized conceptually?

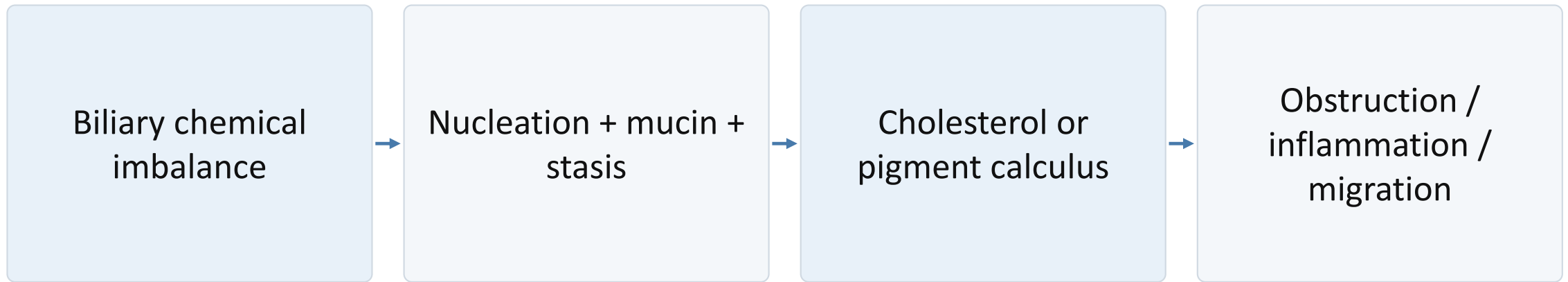
Case application: Infected ductal bile

Several soft, laminated brown calculi are found in the setting of biliary infection.

Interpret the clinicopathologic clues:

- Which stone class is suggested?
- Which microbial enzyme helps generate the insoluble pigment component?

Synthesis: Mechanism, material, consequence



Stone composition explains morphology; Stone location explains clinical manifestations.

References and source boundaries

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026).
- Chapter 18, “Liver and Gallbladder,” gallbladder / cholelithiasis / epidemiology, pp. 794–796.
- All mechanism and clinical claims in this lecture are grounded in the supplied textbook extraction.
- Figures are original editable schematics; no textbook diagnostic images were reproduced.