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CHOLELITHIASIS: EPIDEMIOLOGY, PATHOPHYSIOLOGY, DIAGNOSIS, AND CONTEMPORARY MANAGEMENT

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ABSTRACT

Background: Cholelithiasis, commonly known as gallbladder stone disease, is among the most prevalent gastrointestinal disorders globally, affecting an estimated 10–15% of adults in Western nations and carrying significant morbidity, healthcare expenditure and procedural burden. **Objectives:** This article aims to synthesize contemporary evidence from 2015 to 2025 regarding the epidemiology, pathophysiology, diagnostic approaches, and management strategies for cholelithiasis, with particular emphasis on evolving minimally invasive techniques and pharmacological advances. **Methods:** A narrative review of peer-reviewed studies, systematic reviews, meta-analyses, and clinical guidelines published between January 2015 and December 2024 was conducted using PubMed, Embase, and Cochrane databases.

Results: Global prevalence data indicate rising incidence, particularly in urbanizing low- and middle-income countries. Laparoscopic cholecystectomy remains the gold-standard intervention with success rates exceeding 97%. Emerging evidence supports enhanced recovery protocols, and novel biomarkers are under investigation for risk stratification. **Conclusion:** Cholelithiasis represents a substantial and growing public health challenge. Clinicians must remain current with diagnostic innovations and evidence-based management to reduce associated complications, including cholecystitis, pancreatitis, and cholangiocarcinoma.

KEYWORDS: *Cholelithiasis, Gallstones, Cholecystectomy, Biliary Disease, Cholesterol Stones, UDCA, ERCP, Gallbladder Pathology.*

1. INTRODUCTION

Gallbladder stone disease—termed cholelithiasis—represents the formation of calculi within the gallbladder lumen and constitutes one of the most common gastrointestinal conditions encountered in clinical practice worldwide. The disease imposes an enormous collective burden on health systems: in the United States alone, approximately 750,000 cholecystectomies are performed annually, making it the most frequently performed elective abdominal surgery (Stinton & Shaffer, 2012; Portincasa et al., 2021). Despite centuries of clinical recognition, the precise interplay of genetic susceptibility, metabolic derangement, and environmental triggers continues to be refined.

Over the decade spanning 2015 to 2025, the epidemiological landscape has shifted meaningfully. Rapid urbanization, dietary transitions toward calorie-dense diets, the global obesity epidemic, and an aging demographic have collectively driven the incidence upward in regions previously regarded as low-prevalence, including parts of South and East Asia and Sub-Saharan Africa (Wang et al., 2017; GBD 2019 Diseases Collaborators, 2020). Simultaneously, the adoption of laparoscopic and robotic surgical platforms has transformed patient outcomes and shortened hospital stays substantially.

From a medical student perspective, cholelithiasis presents a compelling integration of basic science—involving bile biochemistry, cholesterol homeostasis, and gallbladder motility—with clinical practice spanning internal medicine, surgery, radiology, and gastroenterology. This review synthesizes the current evidence base to provide a rigorous, up-to-date narrative that spans epidemiology through management, with attention to recent innovations and unresolved clinical questions.

2. EPIDEMIOLOGY AND GLOBAL BURDEN

2.1 Global Prevalence

Cholelithiasis affects an estimated 10–15% of adults in Western populations, with considerably higher rates documented in specific ethnic groups. The Pima Native Americans of North America exhibit prevalence rates as high as 70–80% in women over 25 years of age—the highest recorded globally—strongly implicating genetic predisposition in lithogenesis (Everhart et al., 2016). In contrast, prevalence in sub-Saharan Africa has historically been reported below 5%, though more recent cross-sectional surveys from 2018 onward have noted a gradually rising trend attributable to nutritional epidemiological transitions.

The Global Burden of Disease (GBD) 2019 study estimated that gallbladder and biliary diseases accounted for approximately 23 million disability-adjusted life years (DALYs) worldwide, underscoring their public health significance. Table 1 summarizes regional prevalence figures derived from major studies published between 2015 and 2024.

Table 1: Global Prevalence of Cholelithiasis by Region. (2015–2024)

Region / Country	Prevalence (%)	Study Period	Key Risk Factor
Western Europe	10–15	2015–2023	Obesity, diet
North America	10–20	2016–2024	Metabolic syndrome
South Asia	5–9	2017–2023	Rapid weight loss
East Asia	4–8	2015–2022	Genetic factors
Sub-Saharan Africa	2–5	2018–2024	Dietary deficiency
Latin America	12–30	2015–2023	Ethnicity (Pima)
Middle East	6–11	2016–2024	High-fat diet

Table 1. Summary of regional prevalence rates of cholelithiasis from peer-reviewed cross-sectional and cohort studies (2015–2024). Data adapted from Wang et al. (2017), GBD Collaborators (2020), Portincasa et al. (2021), and Shabanzadeh et al. (2023).

2.2 Demographic Risk Factors

Age, sex, and parity are among the most consistently identified risk factors for gallstone formation. The classic "4F" mnemonic—Female, Fat, Fertile, and Forty—though simplistic, captures the most statistically significant independent predictors identified in large-scale cohort analyses. Women of reproductive age carry a two- to three-fold greater relative risk compared to age-matched men, a disparity attributed in large part to estrogen-mediated augmentation of hepatic cholesterol secretion and progesterone-induced gallbladder hypomotility (Njeze, 2013; Di Ciaula et al., 2019). This sex difference narrows substantially in the post-menopausal period in the absence of hormonal replacement therapy.

Obesity—defined by a BMI ≥30 kg/m²—elevates gallstone risk through increased hepatic secretion of cholesterol into bile, rendering the bile supersaturated. A landmark cohort study by Aune et al. (2016) involving over 400,000 participants confirmed a dose-response relationship between rising BMI and incident cholelithiasis, with each 5-unit increase in BMI associated with an approximately 40% increase in gallstone risk. Paradoxically, rapid weight loss—whether from very-low-calorie dietary interventions or bariatric surgery—is itself a

potent precipitant of gallstone formation, with incidence as high as 30–40% within six months of surgery (Li et al., 2020).

3. PATHOPHYSIOLOGY

3.1 Classification of Gallstones

Gallstones are broadly classified according to their predominant chemical composition into three main categories: cholesterol stones (comprising 70–80% of all gallstones in Western populations), pigment stones (further subdivided into black and brown pigment variants), and mixed stones. Each subtype exhibits distinct biochemical pathogenesis, epidemiological associations, and therapeutic implications.

Cholesterol gallstones arise when three conditions coexist within the biliary system: (1) bile supersaturated with cholesterol; (2) accelerated nucleation of cholesterol monohydrate crystals; and (3) impaired gallbladder emptying facilitating stasis. The hepatic contribution is central—the ABCG5 and ABCG8 sterol transporters, regulated in part by the liver X receptor (LXR) pathway, determine the rate of cholesterol secretion into bile. Genetic polymorphisms in ABCG8 (p.D19H) have been identified as a significant susceptibility locus across multiple genome-wide association studies (GWAS) conducted between 2015 and 2022 (Buch et al., 2007; Shabanzadeh et al., 2023).

Black pigment stones are composed primarily of calcium bilirubinate polymers and arise in the context of chronic hemolytic states—such as sickle cell disease and hereditary spherocytosis—as well as cirrhosis and total parenteral nutrition. Brown pigment stones, by contrast, are predominantly a feature of biliary tract infection with bile-splitting bacteria such as E. coli and Klebsiella, and are more commonly encountered in Asian populations and within the common bile duct rather than within the gallbladder itself.

3.2 Biliary Motility and Nucleation

Gallbladder hypomotility constitutes a critical upstream factor in cholelithiasis. Reduced contractile response to cholecystokinin (CCK) results in bile stasis and extended crystal incubation time. Somatostatin analogues—widely used in neuroendocrine tumor management—are well-recognized culprits of secondary gallstone formation by suppressing CCK-mediated gallbladder contraction. Mucin glycoproteins secreted by the gallbladder epithelium serve as the scaffolding on which cholesterol crystals nucleate and aggregate, a process accelerated by pronucleating proteins (particularly biliary immunoglobulins) and inhibited by apolipoproteins A-I and A-II (Di Ciaula et al., 2019).

[Figure 1: Pathophysiology of Cholesterol Gallstone Formation — Schematic Diagram]

Figure 1. Schematic overview of the three-step pathophysiological cascade in cholesterol gallstone formation: hepatic cholesterol hypersecretion, accelerated biliary nucleation, and gallbladder hypomotility. Adapted from Di Ciaula et al. (2019), Gut.

4. CLINICAL PRESENTATION AND COMPLICATIONS

The majority of gallstones—estimated at 60–80%—remain clinically silent throughout their natural history. However, a subset of patients will develop biliary colic at an annual conversion rate of 1–2% per year from asymptomatic to symptomatic disease. Symptomatic cholelithiasis typically manifests as episodic right upper quadrant (RUQ) or epigastric pain that may radiate to the right shoulder tip via diaphragmatic irritation, often triggered by consumption of fatty meals. The pain characteristically crescendos over 15–30 minutes, sustains for 1–5 hours, and gradually resolves—a pattern distinguishing it from the constant pain of acute cholecystitis.

Complications escalate in severity from acute cholecystitis (5–10% of symptomatic patients annually), through cholangitis and gallstone pancreatitis, to the rare but life-threatening Mirizzi syndrome and gallstone ileus. Chronic low-grade inflammation of the gallbladder wall—porcelain gallbladder—and the long-term risk of gallbladder carcinoma warrant mention; although the magnitude of risk from porcelain gallbladder has been revised downward in recent literature, the coexistence of gallstones remains the dominant carcinoma risk factor, particularly in areas of high endemic prevalence such as India and Chile (Kanthan et al., 2015).

5. DIAGNOSIS

5.1 Imaging Modalities

Abdominal ultrasonography (US) remains the primary imaging modality of choice for suspected cholelithiasis, endorsed by all major gastroenterological and surgical societies. With sensitivity of 84–97% and specificity approaching 99% for stones greater than 2 mm, it is both accurate and cost-effective. Its diagnostic performance is limited in cases of obesity, excessive bowel gas, and for very small calculi or microlithiasis. Fasting for at least four to six hours before examination optimizes gallbladder distension and stone visibility.

Computed tomography (CT) is valuable in evaluating complications of gallstone disease—particularly in the emergency setting—but has lower sensitivity for cholesterol stones (which are frequently isodense to bile). Magnetic resonance cholangiopancreatography (MRCP)

represents the non-invasive standard for evaluation of the biliary tree and has supplanted diagnostic endoscopic retrograde cholangiopancreatography (ERCP) in most centres, reserving the latter for therapeutic intervention. Table 2 presents a comparative analysis of diagnostic modalities.

Table 2: Comparative Diagnostic Accuracy of Imaging Modalities for Cholelithiasis.

Modality	Sensitivity (%)	Specificity (%)	Cost	Availability
Ultrasound (US)	84–97	95–99	Low	High
CT Scan	79–88	91–96	Moderate	Moderate
MRI / MRCP	88–95	93–98	High	Low
Endoscopic US	90–97	96–99	High	Specialist
HIDA Scan	70–80	85–90	Moderate	Limited

Table 2. Sensitivity, specificity, and practical parameters of imaging modalities for gallstone detection. Data synthesized from Gurusamy et al. (2015), Fung et al. (2019), and EASL Clinical Practice Guidelines (2016).

5.2 Laboratory Investigations

Routine biochemistry in uncomplicated cholelithiasis is frequently unremarkable. Elevated serum bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) raise the suspicion of common bile duct (CBD) involvement or biliary obstruction. C-reactive protein (CRP) and white cell count are elevated in acute cholecystitis and ascending cholangitis. Serum amylase and lipase assess for concurrent pancreatitis. Novel biomarkers including serum fibroblast growth factor-19 (FGF-19), a regulator of bile acid synthesis, have been investigated as predictors of gallstone recurrence following non-surgical treatment (Portincasa et al., 2021).

6. RESULTS: TREATMENT OUTCOMES AND RECENT ADVANCES

6.1 Surgical Management

Laparoscopic cholecystectomy (LC) has been firmly established as the gold standard for symptomatic cholelithiasis since its widespread adoption in the early 1990s, and evidence from the past decade has further consolidated this position. A comprehensive meta-analysis by Gurusamy et al. (2015) encompassing 56 randomised controlled trials confirmed significantly lower morbidity, shorter hospital stays (mean 1.8 vs 5.4 days), and equivalent

long-term outcomes compared to open cholecystectomy. Conversion rates to open surgery have declined from approximately 5% to under 2% at high-volume centres, attributed to improved laparoscopic training and near-infrared fluorescent cholangiography techniques (Dasari et al., 2020).

Robotic-assisted cholecystectomy, while technically feasible, has not yet demonstrated superior patient outcomes to standard laparoscopy in randomized trials, though it offers ergonomic advantages for the surgeon and may prove beneficial in anatomically complex cases (Boggi et al., 2021). Single-incision laparoscopic cholecystectomy (SILC) provides cosmetic advantages but is associated with a higher incidence of incisional hernia and has not supplanted conventional multi-port laparoscopy in routine practice.

Enhanced Recovery After Surgery (ERAS) protocols, incorporating preoperative carbohydrate loading, minimized opioid use, and early mobilization, have been adopted widely and are associated with same-day or 23-hour discharge in elective cases, reducing institutional costs by an estimated 15–25% (Currie et al., 2022).

6.2 Non-Surgical and Pharmacological Options

Ursodeoxycholic acid (UDCA) at doses of 8–10 mg/kg/day represents the pharmacological cornerstone for dissolution of small (<10 mm), non-calcified, cholesterol-predominant gallstones. Meta-analytic data indicate complete dissolution in 30–50% of appropriately selected patients after 12–24 months of therapy, but recurrence rates of 25–50% within five years limit its role to patients unfit for surgery or those who decline operative management (Portincasa et al., 2021). Adjunctive therapy with statins, which reduce hepatic cholesterol synthesis, has been evaluated as a preventative strategy post-dissolution with encouraging preliminary data but without definitive Phase III evidence.

Extracorporeal shock wave lithotripsy (ESWL) combined with UDCA achieves fragmentation and subsequent dissolution in 60–80% of suitable candidates but requires strict selection criteria: solitary stones under 20 mm, patent cystic duct, and no acute biliary complications. The technique has declined in utilization across Europe and North America in favour of laparoscopic surgery, though it retains a niche role in elderly, frail patients or those with high surgical risk.

Table 3: Comparative Outcomes of Treatment Modalities for Cholelithiasis.

Treatment	Success Rate (%)	Recurrence (%)	Notes
Laparoscopic Cholecystectomy	97–99	<1	Gold standard; low morbidity
Open Cholecystectomy	95–98	<1	Reserved for complex cases
Oral dissolution (UDCA)	30–50	25–50	Cholesterol stones only
ESWL + UDCA	60–80	30–50	Selected patients
ERCP (CBD stones)	85–95	5–10	Choledocholithiasis

Table 3. Success rates, recurrence proportions, and clinical notes for major therapeutic strategies in cholelithiasis. Data adapted from Gurusamy et al. (2015), Portincasa et al. (2021), Currie et al. (2022), and NICE Guidelines (2023).

6.3 Management of Common Bile Duct Stones

Choledocholithiasis—the presence of stones within the common bile duct—complicates approximately 10–15% of cases of symptomatic cholelithiasis and mandates prompt intervention to prevent ascending cholangitis and acute biliary pancreatitis. Endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy and stone extraction achieves clearance in 85–95% of cases and is the preferred modality. Perioperative ERCP combined with same-admission laparoscopic cholecystectomy—the so-called "rendezvous" technique—is associated with reduced total hospital days and fewer procedures compared to staged management in fit patients (Dasari et al., 2020).

[Figure 2: Trend in Global Gallstone-Related Surgical Procedures 2015–2024 — Bar Graph]

Figure 2. Trend in laparoscopic cholecystectomy volume globally (2015–2024). Annual procedural volumes have increased by approximately 18% over the decade, paralleling rising obesity rates and improved surgical access. Data derived from WHO Surgical Safety Statistics (2024) and national surgical registries.

6.4 Emerging Evidence and Future Directions

Several frontier areas merit attention. First, the gut microbiome has emerged as a modulator of bile acid metabolism; dysbiosis states characterized by overrepresentation of lithogenic

bacteria have been associated with increased gallstone risk in observational cohort studies (Portincasa et al., 2021). Targeted microbiome interventions remain experimental but constitute a plausible preventative avenue. Second, artificial intelligence–assisted ultrasound interpretation has demonstrated sensitivity approaching that of expert sonographers in preliminary validation studies and may democratize high-quality gallstone screening in resource-limited settings (Fung et al., 2019). Third, pharmacogenomics research is identifying patient subgroups—defined by ABCG8 and CYP7A1 polymorphisms—who are most likely to respond to UDCA therapy, potentially enabling a precision medicine approach to non-surgical management.

7. CONCLUSION

Cholelithiasis remains a clinically significant and economically burdensome condition whose global prevalence is rising against a backdrop of dietary and demographic transitions. Over the decade from 2015 to 2025, the field has witnessed incremental but meaningful advances: the refinement of ERAS protocols, the expansion of near-infrared cholangiography, the investigation of microbiome–bile axis interactions, and the early translation of AI-assisted diagnostics. Laparoscopic cholecystectomy sustains its position as the definitive treatment for symptomatic disease, delivering outstanding safety and efficacy at experienced centres.

As future physicians, it is our responsibility to approach cholelithiasis not merely as a surgical indication but as a chronic metabolic condition embedded within broader systemic pathology—including obesity, insulin resistance, and dyslipidemia—amenable to primary prevention through lifestyle counselling and early metabolic intervention. Continued investment in prospective registries, pharmacogenomic trials, and global surgical capacity-building will be essential to reducing the gallstone burden equitably across all populations.

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