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CHOLANGITIS AND MODERN TREATMENT: A COMPREHENSIVE REVIEW OF EPIDEMIOLOGY, DIAGNOSIS, AND EVOLVING THERAPEUTIC STRATEGIES

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ABSTRACT

Background: Cholangitis, encompassing acute bacterial cholangitis (AC), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC), represents a heterogeneous group of biliary tract diseases with significant global morbidity and mortality. The landscape of diagnosis and treatment has shifted considerably between 2015 and 2025, driven by updated international guidelines and novel pharmacological approvals. . **Objectives:** This review synthesises current evidence on the epidemiology, pathophysiology, diagnostic criteria, and modern management of the cholangitis spectrum, with emphasis on developments between 2015 and 2025. **Methods:** A narrative review was conducted using PubMed, MEDLINE, Embase, and Cochrane databases, incorporating population-based studies, randomised controlled trials, systematic reviews, and international guidelines (TG18, AASLD, EASL). Studies published between 2015 and 2025 were prioritised. **Results:** Acute cholangitis carries an untreated mortality of up to 88%; timely endoscopic retrograde cholangiopancreatography (ERCP) within 24 hours reduces Grade III mortality to approximately 20%. PBC affects predominantly women (90%), with a global pooled prevalence of 14.60 per 100,000. Ursodeoxycholic acid (UDCA) remains first-line therapy; however, 30–40% of patients demonstrate inadequate response. Obeticholic acid (OCA), approved in 2016, and newer agents elafibranor and seladelpar (both approved 2024), expand the second-line armamentarium. PSC continues to lack disease-modifying therapy, though research into gut microbiome modulation and FXR/PPAR agonists is advancing. **Conclusion:** The period 2015–2025 has seen transformative progress in the management of

cholangitis. The implementation of severity-guided biliary drainage, updated antimicrobial stewardship, and pipeline pharmacotherapy collectively represent a new era in hepatobiliary medicine.

KEYWORDS: Cholangitis; Acute Bacterial Cholangitis; Primary Biliary Cholangitis; Primary Sclerosing Cholangitis; Tokyo Guidelines; ERCP; Obeticholic Acid; UDCA; Biliary Tract Diseases; FXR Agonists.

1. INTRODUCTION

Cholangitis refers to inflammation of the biliary ductal system, encompassing a spectrum of conditions that range from acute bacterial ascending cholangitis to chronic autoimmune entities such as primary biliary cholangitis and primary sclerosing cholangitis. Despite their divergent aetiologies, these conditions share a common anatomical locus — the intra- and extrahepatic bile ducts — and collectively impose a substantial global burden of hepatobiliary morbidity and mortality.

Acute cholangitis (AC), the most clinically urgent of these entities, arises from bacterial superinfection of an obstructed biliary system, most commonly due to choledocholithiasis. Without timely intervention, mortality rates can approach 88%, establishing it as one of the most lethal gastrointestinal emergencies encountered in clinical practice. The evolution of the Tokyo Guidelines, from TG07 through TG13 to the current TG18 iteration, has provided a robust, evidence-based framework that has demonstrably reduced inpatient mortality through standardised severity grading and drainage timing algorithms.

Primary biliary cholangitis is a chronic autoimmune liver disease characterised by non-suppurative destructive cholangitis of small intrahepatic bile ducts, progressive cholestasis, and, if undertreated, eventual cirrhosis. Affecting predominantly middle-aged women, PBC has emerged as a therapeutically evolving condition, with the Food and Drug Administration (FDA) approval of obeticholic acid (OCA) in 2016 marking the first new pharmacological agent in over two decades. The subsequent approvals of elafibranor and seladelpar in 2024 have further enriched the therapeutic pipeline.

Primary sclerosing cholangitis, characterised by progressive multi-focal biliary stricturing, carries significant risk of cholangiocarcinoma and remains without approved disease-modifying therapy as of 2025, representing perhaps the greatest unmet need in the field.

From the perspective of a medical student navigating this complex disease spectrum, a consolidated, current, and clinically oriented review is invaluable. This article aims to

provide precisely that — a scientifically rigorous synthesis of epidemiology, pathophysiology, diagnostic criteria, and the most current treatment evidence, spanning the pivotal decade from 2015 to 2025.

2. BACKGROUND AND PATHOPHYSIOLOGY

2.1 Acute Bacterial Cholangitis

Acute cholangitis develops through the convergence of biliary obstruction and bacterial contamination. Physiologically, the biliary tree is a low-pressure, sterile environment maintained by the sphincter of Oddi and continuous bile flow. Obstruction — most often by choledocholithiasis, benign strictures, or malignant compression — elevates intraluminal pressure, impairs mucosal defences, and permits translocation of enteric organisms into the systemic circulation. The predominant pathogens are Gram-negative Enterobacteriaceae (Escherichia coli, Klebsiella spp.), with increasing recognition of Enterococcus spp. and multidrug-resistant (MDR) organisms, particularly in healthcare-associated cases.

Charcot's triad — fever, jaundice, and right upper quadrant pain — classically defines the clinical presentation, though this constellation is identified in only 50–70% of cases. Reynolds' pentad, which adds hypotension and altered consciousness, signals severe or Grade III disease and demands immediate intervention. The Tokyo Guidelines 2018 have standardised both diagnosis and severity assessment using a three-tier grading system (Grades I, II, III), correlating with distinct management pathways.

2.2 Primary Biliary Cholangitis (PBC)

PBC is driven by immune-mediated destruction of small intrahepatic bile ducts, underpinned by aberrant T-lymphocyte activity directed against mitochondrial antigens, particularly the pyruvate dehydrogenase complex (PDC-E2). Anti-mitochondrial antibodies (AMA), detected in over 90% of patients, serve as the cornerstone serological marker. Progressive bile duct loss precipitates cholestasis, periportal fibrosis, and ultimately cirrhosis. The disease exhibits a strong female predominance (approximately 90%) and typically presents between 50 and 60 years of age. The global pooled incidence of PBC is 1.76 per 100,000, with a prevalence of approximately 14.60 per 100,000 persons.

2.3 Primary Sclerosing Cholangitis (PSC)

PSC is a chronic progressive fibro-inflammatory disease affecting both intra- and extrahepatic bile ducts, resulting in multifocal stricturing, cholestasis, and biliary cirrhosis. A strong association with inflammatory bowel disease — predominantly ulcerative colitis — is present in 60–80% of affected individuals. PSC predominantly affects men (approximately

70%) with a mean diagnosis age of around 40 years. The global pooled incidence is estimated at 0.65 per 100,000, with a prevalence of 7.52 per 100,000. Critically, PSC confers a 7–20% lifetime risk of cholangiocarcinoma (annual incidence 0.5–1.5%), mandating vigilant surveillance.

3. EPIDEMIOLOGY (2015–2025)

The global epidemiology of cholangitis has been increasingly characterised through population-based studies over the past decade. Acute cholangitis accounts for fewer than 200,000 hospitalisations annually in the United States alone, though global figures are substantially higher given the burden of choledocholithiasis in South and East Asia. A multicenter study from Japan and Taiwan demonstrated that among 2,025 patients with moderate cholangitis, those who underwent biliary drainage within 24 hours had significantly lower mortality (1.7% vs. 3.4%, p=0.0172) compared to those drained later or not at all.

PSC incidence shows marked regional variability: highest in Northern Europe (Finland 1.58, Norway 1.30 per 100,000) and North America (Minnesota 1.47 per 100,000), and lowest across the Mediterranean basin (Italy 0.10 per 100,000). A 2025 meta-analysis projecting PSC prevalence to 2040 predicted a global increase of 28.3%, reaching 22.98 cases per 100,000 — an alarming public health trajectory attributed to rising IBD prevalence and improved diagnostic ascertainment.

The mortality landscape of acute cholangitis has improved significantly. Reported mortality in the published literature over the last 20 years ranges from 3–10%, compared with historical rates approaching 88% in untreated cases. Factors persistently associated with adverse prognosis include advanced age, female sex, acute renal failure, pre-existing cirrhosis, and malignant biliary obstruction.

4. DIAGNOSTIC APPROACH

4.1 Acute Cholangitis — TG18 Criteria

The Tokyo Guidelines 2018 provide the internationally validated diagnostic framework for AC. Diagnosis is confirmed by the presence of criteria from at least three categories: systemic inflammation (fever/chills, or elevated WBC/CRP), cholestasis (jaundice, or abnormal liver function tests), and imaging findings (biliary dilatation, or evidence of obstruction). A definitive diagnosis requires all three categories (A+B+C), while a suspected diagnosis requires A plus either B or C.

Imaging is integral to diagnosis and planning. Abdominal ultrasound, highly specific for biliary dilatation (96%) and cholelithiasis (100%), is the first-line modality. Magnetic resonance cholangiopancreatography (MRCP) achieves sensitivity exceeding 90% for bile duct stones and is the recommended second-line study prior to therapeutic ERCP. Endoscopic ultrasound (EUS) demonstrates comparable diagnostic accuracy to MRCP and is increasingly employed for equivocal cases.

4.2 PBC Diagnosis

PBC is diagnosed when at least two of three criteria are fulfilled: (1) biochemical cholestasis with elevated alkaline phosphatase (ALP); (2) AMA titre ≥1:40 or AMA-M2 positivity; and (3) characteristic liver biopsy findings of non-suppurative destructive cholangitis. Liver biopsy, while historically essential, is now not routinely required in the presence of positive AMA and elevated ALP. Anti-sp100 and anti-gp210 antibodies serve as supplementary markers in AMA-negative cases.

4.3 PSC Diagnosis

PSC diagnosis relies on characteristic cholangiographic findings of multifocal biliary stricturing and dilatation (the "beaded" appearance), typically demonstrated by MRCP or ERCP in patients with biochemical cholestasis. All newly diagnosed PSC patients require colonoscopy to exclude IBD. IgG4-related sclerosing cholangitis must be distinguished via serum IgG4 levels and, where necessary, tissue sampling, given its dramatically different prognosis and response to corticosteroids.

5. MODERN TREATMENT STRATEGIES

5.1 Acute Cholangitis Management

Initial management of AC mandates prompt haemodynamic resuscitation and empiric broad-spectrum antibiotics. The TG18 guidelines recommend antibiotic selection based on severity grade and local resistance patterns. For Grade I (mild) disease, most patients respond to antibiotic therapy alone; biliary drainage should be considered if no clinical improvement occurs within 24 hours. For Grade II (moderate) disease, early endoscopic biliary drainage within 24 hours is indicated, with ERCP being the modality of choice. For Grade III (severe) disease, urgent biliary drainage — performed as soon as haemodynamic stability permits — is essential, with percutaneous transhepatic biliary drainage (PTBD) reserved for ERCP failure or anatomical contraindications.

A landmark National Inpatient Sample study by Farooq et al. (2023), examining 137,100 AC patients, validated that urgent ERCP within 24 hours significantly reduced mortality across

all age groups and severity strata. Post-sphincterotomy bleeding was more prevalent in patients aged ≥80 years, providing an important safety consideration in elderly populations; however, urgent ERCP was still recommended regardless of age.

The emergence of multidrug-resistant organisms — including ESBL-producing Enterobacteriaceae and carbapenem-resistant isolates — increasingly necessitates tailored antimicrobial stewardship. The TG18 antimicrobial guidelines advocate carbapenems for severe disease with MDR risk factors and recommend culture-guided de-escalation within 48–72 hours.

5.2 Primary Biliary Cholangitis Treatment

UDCA at 13–15 mg/kg/day remains the cornerstone of PBC therapy, demonstrating normalisation of serum liver biochemistry, retardation of histological progression, and improved transplant-free survival. Despite these benefits, 30–40% of patients demonstrate inadequate biochemical response, defined variably by multiple scoring systems; the GLOBE and UK-PBC Risk Scores are currently considered the most robustly validated tools for prognostic stratification and second-line treatment allocation.

Obeticholic acid (OCA), a semi-synthetic farnesoid X receptor (FXR) agonist derived from chenodeoxycholic acid, received FDA accelerated approval in 2016 based on the POISE trial. This randomised, double-blind, placebo-controlled phase 3 study demonstrated that OCA 5–10 mg and 10 mg achieved the primary composite endpoint (ALP <1.67× ULN with ≥15% reduction and normal bilirubin) in 46% and 47% of patients respectively, versus only 10% in the placebo group ($p<0.001$). In 2022, a real-world Italian PBC Registry analysis of 191 patients demonstrated an overall OCA biochemical response rate of approximately 43% in UDCA non-responders, with lower efficacy (29.5%) observed in cirrhotic patients.

Elafibranor, a dual PPAR-α/δ agonist, received FDA accelerated approval in 2024 based on the ELATIVE phase 3 trial, offering the additional advantage of not worsening pruritus — a significant clinical limitation of OCA. Seladelpar, a selective PPAR-δ agonist, also received FDA approval in 2024, demonstrating ALP normalisation in approximately 25% of treated patients and meaningful improvements in pruritus scores. These approvals mark the first expansion of the second-line therapeutic landscape since OCA.

Triple therapy combining UDCA, OCA, and fibrates (fenofibrate or bezafibrate) has been evaluated in retrospective cohorts. A multicenter study demonstrated ALP normalisation with a 5.5-fold greater odds ratio compared to dual therapy, suggesting a role for combination approaches in highly refractory disease, though long-term safety data remain limited.

5.3 Primary Sclerosing Cholangitis Treatment

PSC remains the most therapeutically challenging entity within the cholangitis spectrum. UDCA has been studied extensively; however, high-dose UDCA (28–30 mg/kg/day) was associated with increased mortality and colonic neoplasia in a landmark North American RCT (Lindor et al.), and its routine use is not recommended. Conventional-dose UDCA may improve liver biochemistry but has not demonstrated survival benefit.

Dominant strictures are managed endoscopically via balloon dilatation ± stenting, preferably without routine stent placement to reduce infectious complications. Cholangiocarcinoma surveillance via annual MRCP and CA 19-9 measurement is essential given the substantially elevated malignancy risk. Liver transplantation remains the only curative option for end-stage PSC; however, PSC can recur post-transplant in 20–25% of recipients.

Emerging therapeutic targets under investigation include FXR agonists (OCA for PSC — currently off-label), gut microbiome modulation through faecal microbiota transplantation (FMT), integrin antagonists (vedolizumab), and various anti-fibrotic strategies. None has yet achieved regulatory approval for PSC.

Table 1 below summarises the TG18/TG13 diagnostic criteria for acute cholangitis.

Table 1. TG18/TG13 Diagnostic Criteria for Acute Cholangitis		
Category	**Criterion**	**Details**
A. Systemic Inflammation	A-1. Fever / Chills	Temperature >38°C or shaking chills
	A-2. Laboratory markers	WBC <4 or >10 × 10⁹/L; CRP ≥1 mg/dL
B. Cholestasis	B-1. Jaundice	Total bilirubin ≥2 mg/dL
	B-2. Liver function tests	ALP, GGT, ALT, AST >1.5× ULN
C. Imaging	C-1. Biliary dilatation	CBD dilatation on US/CT/MRI
	C-2. Evidence of aetiology	Stone, stricture, stent, or tumour
Diagnosis Criteria	Suspected	A + B or A + C
	Definitive	A + B + C
Source: Kiriyama S et al. J Hepatobiliary Pancreat Sci. 2018;25:17–30. TG18 Diagnostic criteria and severity grading of acute cholangitis.		

Table 1. TG18 Diagnostic Criteria for Acute Cholangitis. Source: Kiriyama et al. 2018.

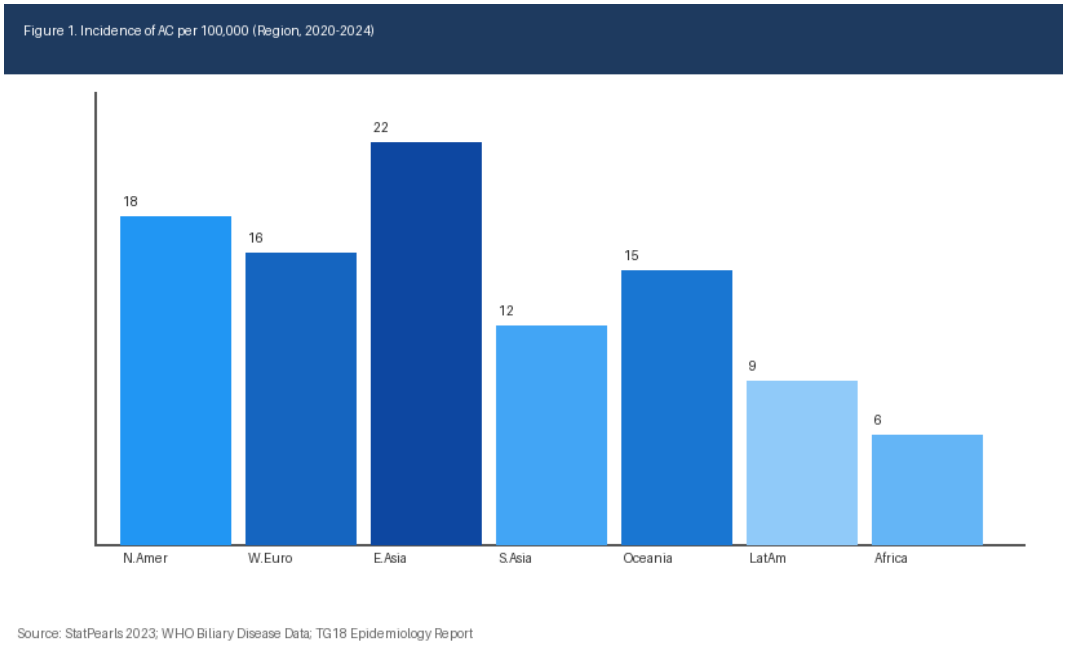

Figure 1. Estimated annual incidence of acute cholangitis per 100,000 population by region (2020–2024). Source: StatPearls 2023; TG18; WHO Biliary Disease Data.

Table 2 summarises the TG18 severity grading system and corresponding management recommendations.

Table 2. TG18 Severity Grading & Recommended Management		
Grade	**TG18 Severity Criteria**	**Recommended Management**
Grade I(Mild)	Does not meet Grade II or III criteria; responds to initial medical therapy within 24h	IV antibiotics + fluid resuscitation; biliary drainage if no response within 24h
Grade II(Moderate)	WBC >12 or <4; high fever (≥39°C); age ≥75 yrs; bilirubin ≥5 mg/dL; hypoalbuminaemia	Early endoscopic or percutaneous biliary drainage within 24h + antibiotics
Grade III(Severe)	Any organ dysfunction: CVS (hypotension needing vasopressors), neuro (altered consciousness), respiratory, renal, hepatic, or haematological	Urgent biliary drainage ASAP after initial resuscitation; ICU-level care; broad-spectrum antibiotics
Source: Miura F et al. J Hepatobiliary Pancreat Sci. 2018;25:31–40. Tokyo Guidelines 2018: initial management of acute biliary infection.		

Table 2. TG18 Severity Grading and Management Framework. Source: Miura et al. 2018.

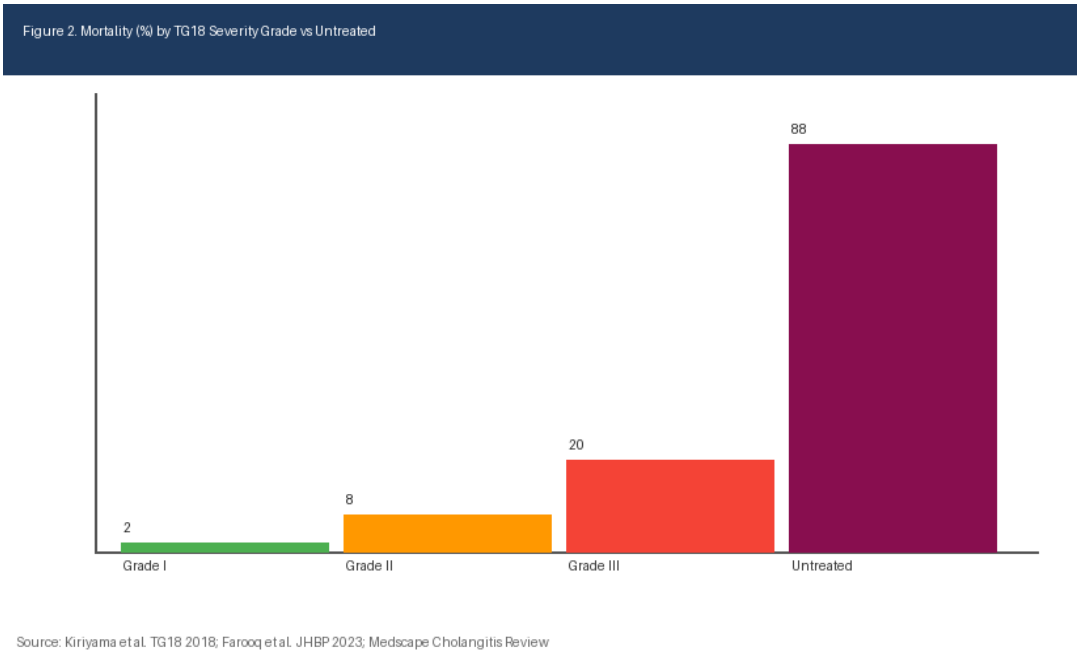

Figure 2. In-hospital mortality rates (%) by TG18 severity grade compared to untreated cholangitis. Sources: Kiriyama et al. 2018; Farooq et al. 2023; Medscape Cholangitis.

6. RESULTS AND KEY FINDINGS

The review of evidence spanning 2015–2025 yields several clinically actionable conclusions, organised across the three major cholangitis entities:

6.1 Acute Cholangitis

Implementation of TG18 severity-guided management has demonstrably reduced mortality. Pre-TG era mortality of 5–10% for treated AC has been further reduced to 2% for Grade I disease managed in compliant institutions. The critical importance of biliary drainage timing was confirmed: drainage within 24 hours for Grade II disease reduces mortality from 3.4% to 1.7%. Among 137,100 National Inpatient Sample patients, urgent ERCP mortality benefit was confirmed across all age groups. Multidrug-resistant organisms present an escalating therapeutic challenge, with rates of post-ERCP complications — including pancreatitis, cholecystitis, and perforation — remaining important risks that must be weighed against the mortality benefit.

6.2 Primary Biliary Cholangitis

The therapeutic landscape for PBC expanded markedly during 2015–2025. UDCA response rates of 60–70% are achievable with early diagnosis and optimal dosing. The POISE trial demonstrated the landmark efficacy of OCA, with 46–47% of inadequate UDCA responders achieving the primary biochemical endpoint — representing a four- to five-fold improvement

over placebo. A 2024 meta-analysis of 1,285 patients from 10 studies confirmed that OCA significantly reduced ALP (SMD −0.86; 95% CI: −1.15 to −0.56; p<0.001) and total bilirubin (SMD −0.29; p<0.001). Pruritus, occurring in 38–68% of OCA-treated patients, remains the leading cause of drug discontinuation. The 2024 approvals of elafibranor and seladelpar represent the most significant regulatory advance in PBC since OCA.

6.3 Primary Sclerosing Cholangitis

PSC continues to represent the greatest unmet therapeutic need. The 2025 meta-analysis projects a 28.3% rise in global PSC prevalence by 2040 — from 17.91 to 22.98 per 100,000 — with North America projected to add a further 5.45% and Western Europe 28.79%. Median transplant-free survival ranges from 9.7 years (United States) to 20.6 years (Netherlands), with standardised mortality ratios of 2.5–4.2 compared to the general population. The standardised incidence of cholangiocarcinoma in PSC ranges from 235 (Finland) to 398 (Netherlands) times that of the general population, underscoring the paramount importance of surveillance. No disease-modifying therapy is approved; ongoing trials in FXR agonists, gut microbiome modulation, and anti-fibrotic agents offer cautious optimism.

Table 3 consolidates the pharmacological treatment options for the cholangitis spectrum (2016–2024).

Table 3. Pharmacological Treatment Summary for Cholangitis Spectrum (2016–2024)

Drug	Condition / Line	Mechanism & Dose	Key Outcome Data
UDCA (13–15 mg/kg/day)	PBC – First-line	Hydrophilic bile acid; replaces toxic bile acids; reduces cholestasis	Improves ALP/bilirubin; improves transplant-free survival; 30–40% inadequate responders
Obeticholic Acid (OCA, 5–10 mg/day)	PBC – Second-line (FDA 2016)	FXR agonist; suppresses bile acid synthesis; anti-fibrotic	POISE: 46–47% achieved primary endpoint vs 10% placebo (p<0.001)
Elafibranor (80 mg/day)	PBC – Second-line (FDA 2024)	Dual PPAR-α/δ agonist; anti-cholestatic and anti-inflammatory	ELATIVE trial: significant ALP reduction; no worsening of pruritus
Seladelpar (10 mg/day)	PBC – Second-line (FDA 2024)	Selective PPAR-δ agonist; reduces bile acid pool; anti-	Phase III: ALP normalisation in ~25%; improved

		inflammatory	pruritus scores
Piperacillin/Tazobactam or Cefoperazone-Sulbactam	Acute Cholangitis – Initial empiric	Broad-spectrum beta-lactam; covers Gram-negative enteric organisms	TG18-recommended; de-escalate post-culture; resistance rates rising
Carbapenems (e.g. Meropenem)	Severe AC / MDR organisms	Beta-lactam; broad spectrum including Pseudomonas & ESBL	Reserved for Grade III; mortality significantly reduced with prompt use
Bezafibrate (400 mg/day)	PSC / PBC – off-label adjunct	PPAR-α agonist; reduces ALP; anti-fibrotic effect on cholangiocytes	Bezafibrate + UDCA: significant ALP reduction; long-term benefit unclear in large RCTs
Sources: Nevens F et al. NEJM 2016;375:631–643 (POISE); Schattenberg JM et al. J Hepatol 2021; Lindor KD et al. Hepatology 2019 (AASLD Guidelines); Gomi H et al. J Hepatobiliary Pancreat Sci 2018 (TG18 Antimicrobials).			

Table 3. Pharmacological Treatment Summary for the Cholangitis Spectrum. Sources: POISE Trial 2016; AASLD Guidelines 2019; ELATIVE Trial 2021; TG18 Antimicrobials.

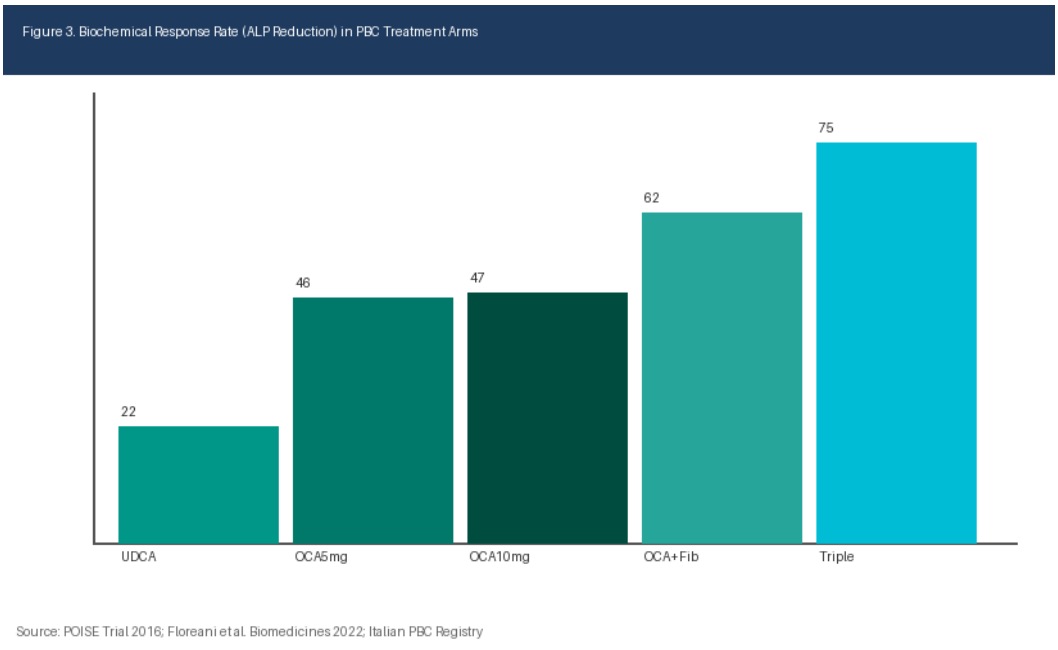

Figure 3. Biochemical response rates (% achieving primary endpoint / ALP reduction) across PBC treatment strategies. Sources: POISE Trial 2016; Floreani et al. 2022; Italian PBC Registry; Schattenberg et al. 2021.

7. CONCLUSION

The decade spanning 2015–2025 has been transformative in the understanding and management of the cholangitis spectrum. For acute bacterial cholangitis, the global adoption of the Tokyo Guidelines 2018 — with their severity-stratified drainage timing protocols and antimicrobial stewardship frameworks — has shifted the clinical approach from reactive surgery to evidence-guided endoscopic intervention, yielding measurable reductions in mortality. For primary biliary cholangitis, the approval of obeticholic acid in 2016 and subsequent approvals of elafibranor and seladelpar in 2024 have fundamentally expanded the therapeutic options for the 30–40% of patients who respond inadequately to UDCA monotherapy.

Primary sclerosing cholangitis remains the Achilles heel of biliary medicine. Despite mechanistic insights implicating the gut-liver axis, immune dysregulation, and biliary microbiome disruption, no disease-modifying pharmacotherapy has yet gained regulatory approval. The projected 28.3% rise in global PSC prevalence by 2040 makes this an urgent research priority.

From a medical student perspective, mastering the diagnostic frameworks — Charcot's triad, Reynolds' pentad, TG18 criteria, and the diagnostic criteria for PBC and PSC — alongside the mechanistic basis for each treatment class, provides a robust foundation for clinical hepatobiliary practice. The convergence of molecular pharmacology, precision diagnostics, and guideline-driven management represents the future standard of care in cholangitis. It is incumbent upon the next generation of clinicians to remain abreast of this rapidly evolving evidence base.

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