Pancreatic duct calculi: pathophysiology and management

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Purpose of review
Pancreatic ductal calculi (PDC) are a defining feature of chronic pancreatitis and contribute significantly to morbidity through pain and ductal obstruction. This review provides a timely update on the evolving understanding of PDC pathogenesis and highlights current and emerging strategies for their management.

Recent findings
Stone formation in chronic pancreatitis is multifactorial, involving altered pancreatic juice composition, reduced lithostatic proteins, genetic predispositions, and environmental risk factors such as alcohol and smoking. Advances in endoscopic techniques, particularly the combination of extracorporeal shock wave lithotripsy (ESWL) and endoscopic retrograde cholangiopancreatography (ERCP), have improved ductal clearance and symptom control. Pancreatoscopy-guided lithotripsy is gaining traction in complex cases. Surgical options such as longitudinal pancreatojejunostomy and head resection remain vital in patients with extensive disease or failed endoscopic therapy, with evidence supporting superior long-term pain relief when performed early.

Summary
Management of PDC requires a multidisciplinary, personalized approach. Endoscopic therapy is the first-line intervention in most cases, while surgery offers durable benefits in select patients. Future directions include identifying biomarkers for early intervention, refining patient selection, and exploring pharmacological strategies to prevent stone formation and recurrence.

Keywords
chronic pancreatitis, endoscopic retrograde cholangiopancreatography, extracorporeal shock wave lithotripsy, pancreatic duct calculi

INTRODUCTION

Chronic pancreatitis is an inflammatory condition characterized by fibrosis, scarring, and dystrophic calcification of the pancreas [1]. A key pathological feature of this condition is the formation of stones within the pancreatic ductal system. These stones, also known as pancreatic stones, pancreatic calculi, or pancreatolithiasis, typically form within the major and side branch ducts [2]. Therefore, the term pancreatic ductal calculi (PDC) is more accurate.

The prevalence of PDC in chronic pancreatitis is approximately 50%, regardless of the underlying etiology [2,3]. Incidence increases with disease duration and may approach nearly 90% [4]. The formation of PDC and strictures marks a point of irreversibility in the natural course of chronic pancreatitis, leading to upstream ductal dilation and increased pancreatic pressure, major contributors to the hallmark symptom of pain [5] (Fig. 1).

Managing PDC is complex and often necessitates a stepwise, multidisciplinary approach. While medical therapy is largely investigational, advances in endoscopic techniques particularly when paired with extracorporeal shock wave lithotripsy (ESWL) have revolutionized the management of PDC in select patients. In refractory or extensive disease, surgical interventions such as lateral pancreaticojejunostomy and pancreatic head resections offer long-term relief [6]. This review aims to provide a comprehensive overview of the pathogenesis and management of PDC in chronic pancreatitis, integrating current evidence,

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KEY POINTS

- Pancreatic ductal calculi (PDC) are a hallmark of chronic pancreatitis, contributing significantly to ductal obstruction, pain, and disease progression.
- Endoscopic therapy combined with extracorporeal shock wave lithotripsy (ESWL) achieves effective ductal clearance and pain relief in the majority of symptomatic patients.
- Emerging techniques like pancreatoscopy-guided lithotripsy offer promising alternatives for complex or refractory PDC cases.
- Surgical intervention provides superior long-term pain relief compared to endoscopic approaches, especially in patients with extensive disease or pancreatic head involvement.
- A multidisciplinary, individualized treatment strategy is critical to optimize outcomes and preserve pancreatic function in patients with PDC.

emerging therapies, and expert consensus to guide clinical practice.

PATHOGENESIS

PDC reflect longstanding intraductal inflammation, ductal obstruction, and parenchymal fibrosis. The pathogenesis of stone formation is multifactorial and begins with alterations in pancreatic juice composition. Under physiological conditions, pancreatic juice is rich in bicarbonate and lithostatic proteins like pancreatic stone protein (PSP or lithostathine), which inhibit calcium carbonate crystallization [7]. In chronic pancreatitis, recurrent inflammation and acinar cell injury, reduce PSP secretion, promoting supersaturation of pancreatic juice with calcium and other inorganic ions, favouring crystal nucleation and aggregation within the ducts [8,9].

Oxidative stress, alcohol toxicity, and smoking are key environmental contributors to this process, often exacerbating inflammation and increasing ductal permeability, further altering the ionic milieu of pancreatic secretions [10]. Additionally, genetic mutations, such as those in the *SPINK1*, *PRSS1*, and *CFTR* genes, have been associated with enhanced susceptibility to calcific CP, particularly in younger individuals or those with idiopathic CP [11]. The calcific deposits begin as proteinaceous plugs within the small ductules, which progressively enlarge and calcify to form PDC [12]. These stones may obstruct major ducts, raising intraductal pressure and exacerbating pain and acinar cell injury resulting in a vicious cycle contributing to disease progression [5].

Beyond the ductal environment, local pancreatic acidosis secondary to inflammation and ischemia further contributes to crystal formation by impairing bicarbonate secretion and decreasing the solubility of calcium salts [13,14]. Additionally, chronic inflammation leads to fibrosis and loss of functional parenchyma, limiting the buffering capacity of pancreatic secretions and promoting a milieu conducive to lithogenesis [15–17]. These pathophysiological processes underscore the complexity of PDC formation and highlight the need for early identification and management to mitigate complications associated with ductal obstruction due to PDC (Fig. 2).

MANAGEMENT

Indications for intervention

The management of PDC in chronic pancreatitis is guided by a combination of symptom burden,

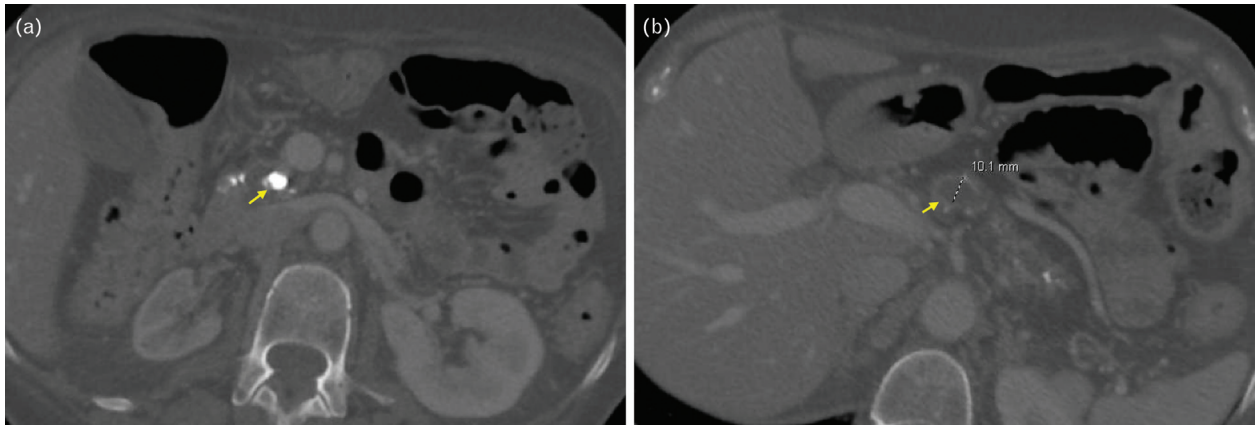

FIGURE 1. Computed tomographic images depicting: (a) A radio-dense PDC in the pancreatic head, and (b) Upstream pancreatic duct dilation.

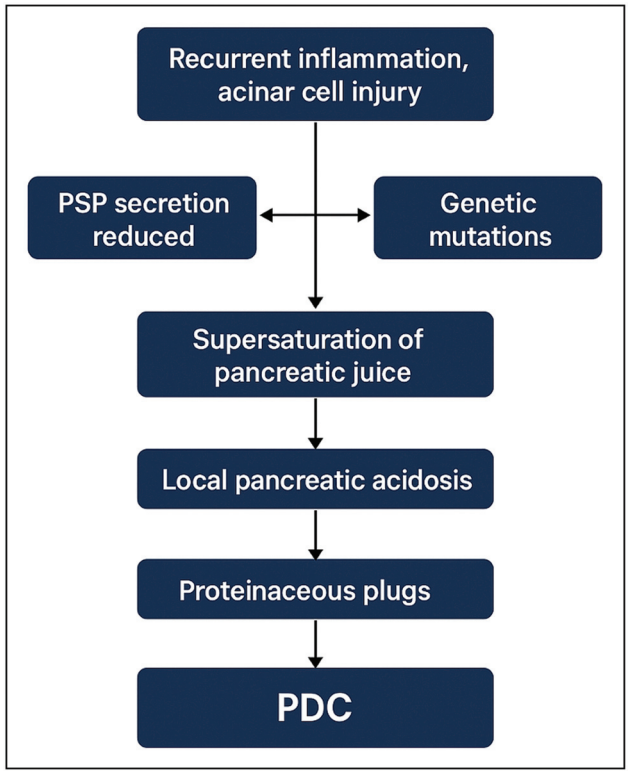

FIGURE 2. Proposed pathogenesis of pancreatic ductal calculi formation.

anatomical considerations, and overall pancreatic function. Intervention is primarily indicated in patients experiencing intractable abdominal pain due to ductal hypertension caused by obstructive calculi. Persistent pain is often linked to a dilated main pancreatic duct (≥5 mm) and the presence of large intraductal stones (>5 mm) in the head or body of the pancreas [18]. Additional indications include recurrent attacks of acute pancreatitis superimposed on chronic pancreatitis and pancreatic exocrine insufficiency unresponsive to enzyme supplementation from obstructive PDC [19].

Medical management

Medical management plays an adjunctive role, aiming to relieve symptoms, prevent recurrence, and support pancreatic function. Pain management includes the use of nonopioid analgesics, with escalation to neuropathic agents such as pregabalin or tricyclic antidepressants if needed. Pancreatic enzyme replacement therapy (PERT) is prescribed to suppress pancreatic secretion and reduce intraductal pressure by negative feedback inhibition of cholecystokinin, thereby potentially alleviating pain and addressing exocrine insufficiency [20]. However, the efficacy of PERT in pain relief remains controversial and appears limited to a subset of patients with small duct disease [21].

Antioxidant therapy with combinations of selenium, beta-carotene, vitamin C, vitamin E, and methionine have been explored as a strategy to mitigate oxidative stress and inflammation in chronic pancreatitis [22]. Some studies suggest modest improvement in pain scores and quality of life, though findings are inconsistent and long-term benefit remains unclear [23,24]. Citrate compounds (such as potassium citrate) have been investigated for their potential to increase calcium solubility in pancreatic juice and dissolve PDC [25]. Small clinical trials have suggested a modest reduction in stone size and recurrence rate, though these findings have not been universally replicated [26]. Lifestyle modifications, including strict abstinence from alcohol and smoking, are crucial as both are independent risk factors for disease progression and stone recurrence [27,28].

Endoscopic management

Endoscopic therapy, particularly via endoscopic retrograde cholangiopancreatography (ERCP), has become the preferred first-line interventional modality for symptomatic PDC located in the head or body of the pancreas. The principal aim is to relieve ductal obstruction, achieve pain resolution and prevent recurrent episodes of inflammation while preserving function. The standard technique involves pancreatic sphincterotomy followed by stone retrieval using extraction balloons or Dormia baskets [29▪].

However, many PDC are large (>5 mm), impacted, or located upstream in a tortuous ductal system, making direct extraction difficult. In such cases, ESWL is employed to fragment stones into smaller pieces before endoscopic removal [30]. ESWL, introduced for pancreatic indications in the 1980 s, is noninvasive and uses focused shock waves to disrupt calcified stones. It is particularly effective in cases with radiopaque stones and a visible pancreatic duct on imaging. ESWL achieves complete ductal clearance in up to 60–70% of patients and partial clearance in up to 90% [31]. Multiple sessions may be required depending on stone density and burden. Following successful fragmentation, ERCP is repeated for retrieval and/or pancreatic duct stenting if there is residual obstruction or ductal stricture. A systematic review comparing ESWL with ERCP showed promising results in favour of ESWL with complete ductal clearance in 69.8%, pain resolution in 64.2% and complete stone fragmentation in 86.3% [32]. Pancreatic stents may be placed temporarily to facilitate drainage and prevent restenosis, especially in patients with residual stones or associated strictures. A randomized clinical trial (RCT) showed increased costs without improved outcomes

by the use of a combination of ERCP and ESWL, therefore, it is reasonable to recommend ERCP only when there is failure of spontaneous stone clearance following ESWL [33].

Emerging endoscopic modalities such as intraductal lithotripsy using electrohydraulic or laser probes, guided by digital single operator peroral pancreatoscopy, offer an alternative for patients in whom ESWL is unsuccessful or unavailable. Although technically challenging and currently limited to high-volume centres, pancreatoscopy-guided lithotripsy has shown promise in achieving targeted stone fragmentation and ductal clearance. Its potential to obviate surgery in select cases is being actively investigated [34]. A recent metanalysis that evaluated pancreatoscopy-guided lithotripsy of PDC showed pooled clearance rates of 81%, clinical success rates of 90% and adverse event rates of 12% [35▪]. Despite the differences in mechanisms, electrohydraulic and laser therapies did not show any differences in terms of technical success [36]. In a meta-analysis comparing pancreatoscopy-guided lithotripsy vs. ESWL, the pooled success rate of pancreatoscopy-guided lithotripsy was 88.1% and that of ESWL was 85.5%. No significant difference was noted among the two modalities in terms of the incidence of adverse events and post intervention pancreatitis [37▪]. A major advantage of pancreatoscopy-guided intervention is the potential for single session fragmentation as compared to ESWL, that often requires multiple sessions and follow up ERCPs for ductal clearance. However, there are no randomized trials comparing the two modalities and future research must strive to fill this lacuna.

Despite its benefits, endoscopic therapy has inherent limitations. Anatomical variations, stone burden, and technical challenges may preclude complete clearance in a subset of patients. Additionally, recurrence of stones and strictures remains a concern, mandating long-term follow-up. Pain relief following endoscopic therapy is achieved in approximately 50–65% of patients, with the best outcomes observed in those with complete ductal clearance and a dilated main pancreatic duct [31].

Surgical management

Surgery is generally reserved for patients with persistent symptoms despite optimal endoscopic management, those with large stone burden extending beyond the reach of endoscopy, coexistent inflammatory mass in the pancreatic head, or suspicion of malignancy. The primary goal of surgery is to decompress the main pancreatic duct, relieve pain, and preserve as much exocrine and endocrine function as possible. A systematic review and metanalysis showed higher pain relief with early surgery compared to endoscopic interventions [odds ratio (OR) 0.46, 95% confidence interval (95% CI) 0.27–0.80, $P = 0.01$] among chronic pancreatitis patients [38].

The Puestow procedure (longitudinal pancreatojejunostomy) is the most commonly performed surgery for ductal decompression in patients with a dilated main pancreatic duct. It involves opening the duct along its length and anastomosing it to a Roux-en-Y limb of the jejunum, allowing for drainage of multiple stones and dilated side branches. For patients with an associated inflammatory mass in the pancreatic head, hybrid procedures such as the Frey procedure (local head coring + longitudinal pancreatojejunostomy) or Beger procedure (duodenum-preserving pancreatic head resection) are preferred. These surgeries offer pain relief while preserving duodenal continuity and pancreatic function. The Whipple procedure (pancreaticoduodenectomy) is rarely needed but may be necessary in cases of suspected neoplasia or extensive disease.

Surgical approaches have shown superior long-term pain relief and lower recurrence compared to endoscopic therapy in randomized trials [39–42]. However, they come with greater perioperative risks and require careful patient selection. Multidisciplinary discussions involving gastroenterologists, pancreatic surgeons, and interventional endoscopists are essential to personalize treatment.

CONCLUSION

PDC represent a defining feature of chronic pancreatitis, arising from complex interactions between genetic, environmental, and inflammatory factors that disrupt the normal composition and flow of pancreatic juice. Their presence is closely linked with ductal obstruction, pain, and disease progression, making timely identification and appropriate management critical. While medical therapy plays a supportive role, definitive treatment for symptomatic PDC often necessitates endoscopic or surgical intervention based on stone burden, ductal anatomy, and symptom severity. Endoscopic approaches, particularly when combined with ESWL, offer effective and minimally invasive options for ductal clearance in most patients. Surgery remains indispensable for those with refractory disease or extensive pancreatic head involvement and has demonstrated durable pain relief and long-term efficacy (Fig. 3). A multidisciplinary, individualized strategy that balances symptom control, functional preservation, and procedural risk is essential to optimize outcomes in patients with PDC in chronic pancreatitis. Future research focusing on early detection, novel dissolution therapies, and prevention of stone recurrence

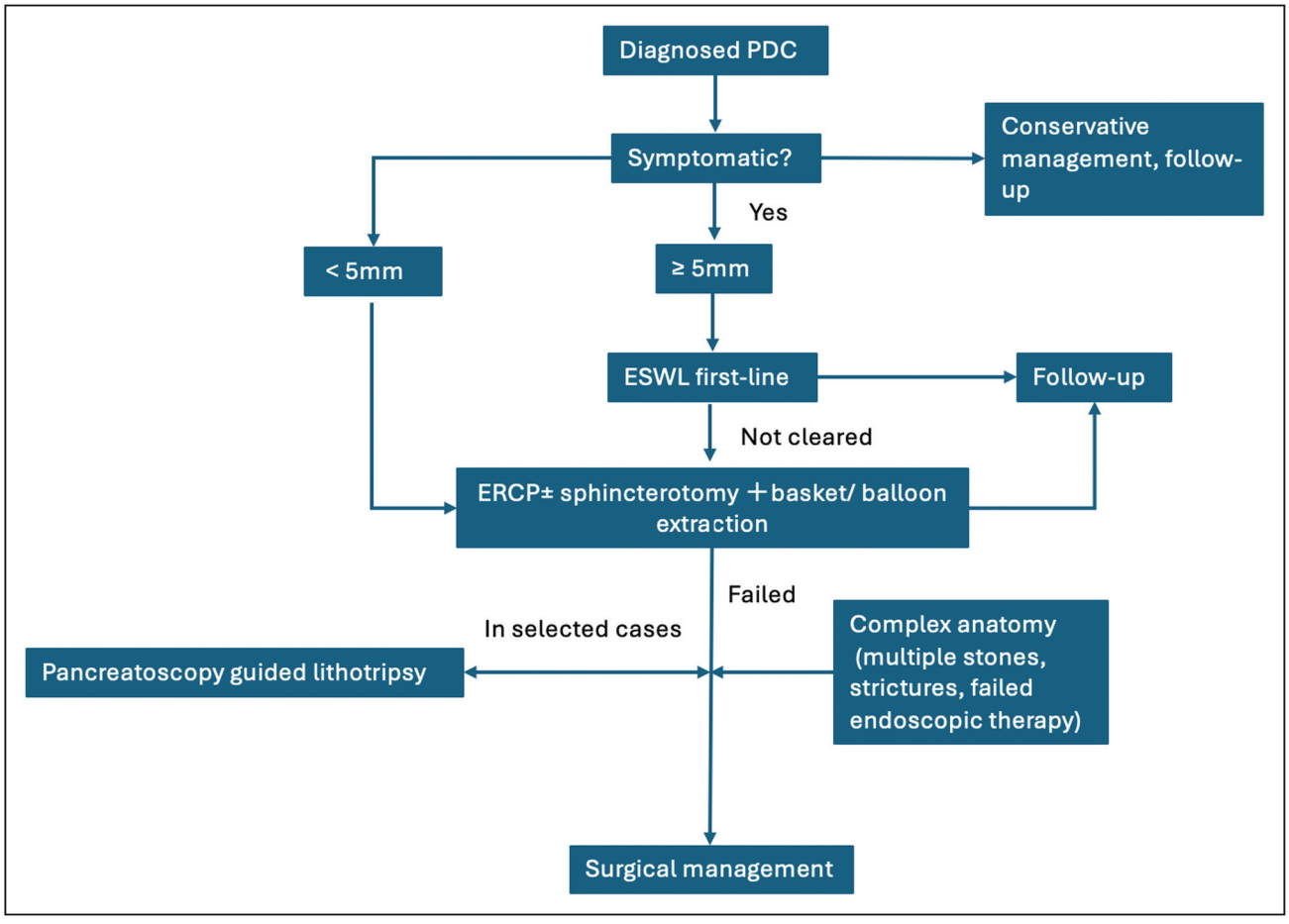

FIGURE 3. Proposed algorithm for the management of pancreatic ductal calculi.

may further enhance care and quality of life in this challenging patient population.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Thierens N DE, Verdonk RC, Löhr JM, *et al.* Chronic pancreatitis. Lancet 2024; 404:2605–2618.
2. Tandan M, Reddy DN, Talukdar R, *et al.* Long-term clinical outcomes of extracorporeal shockwave lithotripsy in painful chronic calcific pancreatitis. Gastrointest Endosc 2013; 78:726–733.
3. Rösch T, Daniel S, Scholz M, *et al.* Endoscopic treatment of chronic pancreatitis: a multicenter study of 1000 patients with long-term follow-up. Endoscopy 2002; 34:765–771.
4. Gardner TB, Adler DG, Forsmark CE, *et al.* ACG Clinical Guideline: chronic pancreatitis. Am J Gastroenterol 2020; 115:322–339.
5. Singh A, Bush N, Bhullar FA, *et al.* Pancreatic duct pressure: a review of technical aspects and clinical significance. Pancreatology 2023; 23:858–867.
6. Tandan M, Talukdar R, Reddy DN. Management of pancreatic calculi: an update. Gut Liver 2016; 10:873–880.
7. Bimmler D, Graf R, Scheele GA, Frick TW. Pancreatic stone protein (lithostathine), a physiologically relevant pancreatic calcium carbonate crystal inhibitor? J Biol Chem 1997; 272:3073–3082.
8. Jin CX, Hayakawa T, Ko SBH, *et al.* Pancreatic stone protein/regenerating protein family in pancreatic and gastrointestinal diseases. Intern Med 2011; 50:1507–1516.
9. Goudshelwar R, Adimoolam BM, Lakhtakia S, *et al.* Alterations in the pH of pancreatic juice are associated with chymotrypsin C inactivation and lithostathine precipitation in chronic pancreatitis patients: a proteomic approach. Clin Proteomics 2022; 19:49.
10. Robles L, Vaziri ND, Ichii H. Role of oxidative stress in the pathogenesis of pancreatitis: effect of antioxidant therapy. Pancreat Disord Ther 2013; 3:112.
11. Zou W, Tang XY, Zhou DZ, *et al.* SPINK1, PRSS1, CTRC, and CFTR genotypes influence disease onset and clinical outcomes in chronic pancreatitis. Clin Transl Gastroenterol 2018; 9:204.
12. Javadi S, Menias CO, Korivi BR, *et al.* Pancreatic calcifications and calcified pancreatic masses: pattern recognition approach on CT. Am J Roentgenol 2017; 209:77–87.
13. Soong C. Intramucosal acidosis and the inflammatory response in acute pancreatitis. Am J Gastroenterol 1999; 94:2423–2429.
14. Steer ML, Waxman I, Freedman S. Chronic pancreatitis. N Engl J Med 1995; 332:1482–1490.
15. Novak I, Haanes KA, Wang J. Acid-base transport in pancreas–new challenges. Front Physiol 2013; 4:380.

16. Behrendorff N, Floetenmeyer M, Schwiening C, Thorn P. Protons released during pancreatic acinar cell secretion acidify the lumen and contribute to pancreatitis in Mice. Gastroenterology 2010; 139
17. Goudshelwar R, Adimoolam BM, Lakhtakia S, *et al.* Alterations in the pH of pancreatic juice are associated with chymotrypsin C inactivation and lithostathine precipitation in chronic pancreatitis patients: a proteomic approach. Clin Proteomics 2022; 19:49.
18. Strand DS, Law RJ, Yang D, Elmunzer BJ. AGA Clinical Practice Update on the endoscopic approach to recurrent acute and chronic pancreatitis: expert review. Gastroenterology 2022; 163:1107–1114.
19. Huang W, de la Iglesia-García D, Baston-Rey I, *et al.* Exocrine pancreatic insufficiency following acute pancreatitis: systematic review and meta-analysis. Dig Dis Sci 2019; 64:1985.
20. Löhr JM, Dominguez-Munoz E, Rosendahl J, *et al.* United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). United Eur Gastroenterol J 2017; 5:153.
21. Hobbs PM, Johnson WG, Graham DY. Management of pain in chronic pancreatitis with emphasis on exogenous pancreatic enzymes. World J Gastrointest Pharmacol Ther 2016; 7:370.
22. Talukdar R, Lakhtakia S, Reddy DN, *et al.* Ameliorating effect of antioxidants and pregabalin combination in pain recurrence after ductal clearance in chronic pancreatitis: results of a randomized, double blind, placebo-controlled trial. J Gastroenterol Hepatol 2016; 31:1654–1662.
23. Hyun Ko K, Min An J, Seo Son M, *et al.* Antioxidant therapy in chronic pancreatitis–promises and pitfalls. Ann Transl Med 2019; 7 (Suppl 3):S115.
24. Siriwardena AK, Mason JM, Sheen AJ, *et al.* Antioxidant therapy does not reduce pain in patients with chronic pancreatitis: the ANTICIPATE study. Gastroenterology 2012; 143 .
25. Jiang X, Zou W, Liao Z. Chemical therapy for chronic pancreatitis: an assumption or an alternative? J Transl Int Med 2022; 10:304–307.
26. De Caro A, Lohse J, Sarles H Characterization of a protein isolated from pancreatic calculi of men suffering from chronic calcifying pancreatitis. Biochem Biophys Res Commun 1979; 87: 1176–1182.
27. Singhvi A, Yadav D. Myths and realities about alcohol and smoking in chronic pancreatitis. Curr Opin Gastroenterol 2018; 34:355.
28. Coté GA, Yadav D, Slivka A, *et al.* Alcohol and smoking as risk factors in an epidemiology study of patients with chronic pancreatitis. Clin Gastroenterol Hepatol 2011; 9:266–273.
29. ■ Ito K, Takuma K, Okano N, *et al.* Current status and future perspectives for endoscopic treatment of local complications in chronic pancreatitis. Dig Endosc 2024; 37:219.

The study highlights advances in endoscopic treatment of chronic pancreatitis complications, showing a shift towards minimally invasive, frontline therapies and outlining future innovations in personalized care and device technology.

30. Dumonceau JM, Delhaye M, Tringali A, *et al.* Endoscopic treatment of chronic pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Updated August. Endoscopy 2019; 51:179–193.
31. Moole H, Jaeger A, Bechtold ML, *et al.* Success of extracorporeal shock wave lithotripsy in chronic calcific pancreatitis management: a meta-analysis and systematic review. Pancreas 2016; 45:651–658.
32. van Huijgevoort NCM, Veld JV, Fockens P, *et al.* Success of extracorporeal shock wave lithotripsy and ERCP in symptomatic pancreatic duct stones: a systematic review and meta-analysis. Endosc Int Open 2020; 8:E1070–E1085.
33. Dumonceau JM, Costamagna G, Tringali A, *et al.* Treatment for painful calcified chronic pancreatitis: extracorporeal shock wave lithotripsy versus endoscopic treatment: a randomised controlled trial. Gut 2007; 56:545–552.
34. Saghir SM, Mashiana HS, Mohan BP, *et al.* Efficacy of pancreatoscopy for pancreatic duct stones: a systematic review and meta-analysis. World J Gastroenterol 2020; 26:5207–5219.
35. ■ Huang P, Khizar H, Song W, Yang J. Pancreatoscopy-guided lithotripsy for pancreatic duct stones: a systematic review and meta-analysis. Turk J Gastroenterol 2024; 35:811–821.

This systematic review and meta-analysis evaluates the efficacy and safety of pancreatoscopy-guided lithotripsy for pancreatic duct stones, demonstrating its growing role as a targeted, minimally invasive option for managing obstructive chronic pancreatitis.

36. Guzmán-Calderón E, Martinez-Moreno B, Casellas JA, Aparicio JR. Per-oral pancreatoscopy-guided lithotripsy for the endoscopic management of pancreatolithiasis: a systematic review and meta-analysis. J Dig Dis 2021; 22: 572–581.
37. ■ Siranart N, Kozai L, Simadibrata DM, *et al.* Per-oral pancreatoscopy guided lithotripsy versus extracorporeal shock wave lithotripsy in pancreatic stone: a meta-analysis. Dig Dis Sci.2025. doi:10.1007/S10620-025-08952-W

This meta-analysis compares per-oral pancreatoscopy-guided lithotripsy with ESWL for pancreatic stones, offering important insights into optimizing treatment choices for obstructive chronic pancreatitis.

38. Boregowda U, Echavarria J, Umapathy C, *et al.* Endoscopy versus early surgery for the management of chronic pancreatitis: a systematic review and meta-analysis. Surg Endosc 2022; 36:8753–8763.
39. Issa Y, Kempeneers MA, Bruno MJ, *et al.* Effect of early surgery vs endoscopy-first approach on pain in patients with chronic pancreatitis: the ESCAPE randomized clinical trial. JAMA 2020; 323:237–247.
40. Jiang L, Ning D, Cheng Q, Chen XP. Endoscopic versus surgical drainage treatment of calcific chronic pancreatitis. Int J Surg 2018; 54:242–247.
41. Díte P, Ružicka M, Zboril V, Novotný I. A prospective, randomized trial comparing endoscopic and surgical therapy for chronic pancreatitis. Endoscopy 2003; 35:553–558.
42. Cahen DL, Gouma DJ, Nio Y, *et al.* Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. N Engl J Med 2007; 356:676–684.