

# Updates in the Management of Chronic Pancreatitis

## Navigating Through Recent Advances



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### KEYWORDS

- Chronic pancreatitis • Management • Therapy • Endoscopy • Surgery
- Nutritional support

### KEY POINTS

- Management necessitates interdisciplinary approach, and patients should have at least annual evaluations to assess causal risk factors, symptom control, and disease-related complications.
- Interventional endoscopy and surgery offer effective and long-lasting symptomatic treatment for selected patients, and these should be performed by experts at comprehensive centers, with early treatment discussions involving all relevant specialists.
- As of now, total pancreatectomy with islet cell autotransplantation offers the only “curative” therapy, but novel therapeutic avenues involving causative treatments are being investigated.

### INTRODUCTION AND BACKGROUND

In recent decades, the management of chronic pancreatitis (CP) has shifted from traditional surgical drainage and partial resection interventions to comprehensive, multidisciplinary approaches.<sup>1</sup> The multidisciplinary approach now includes a wide range of options, from medication, nutritional support, and evolving endoscopic procedures to expanded surgical techniques and, more recently, the exploration of innovative therapies.<sup>2–4</sup> We seek to summarize the current approaches to managing CP, with a particular emphasis on recent advances.

### UPDATES IN MANAGEMENT STRATEGIES

The treatment of CP has evolved significantly, moving from primarily surgical drainage and resection to a multidisciplinary approach that incorporates medical therapy,

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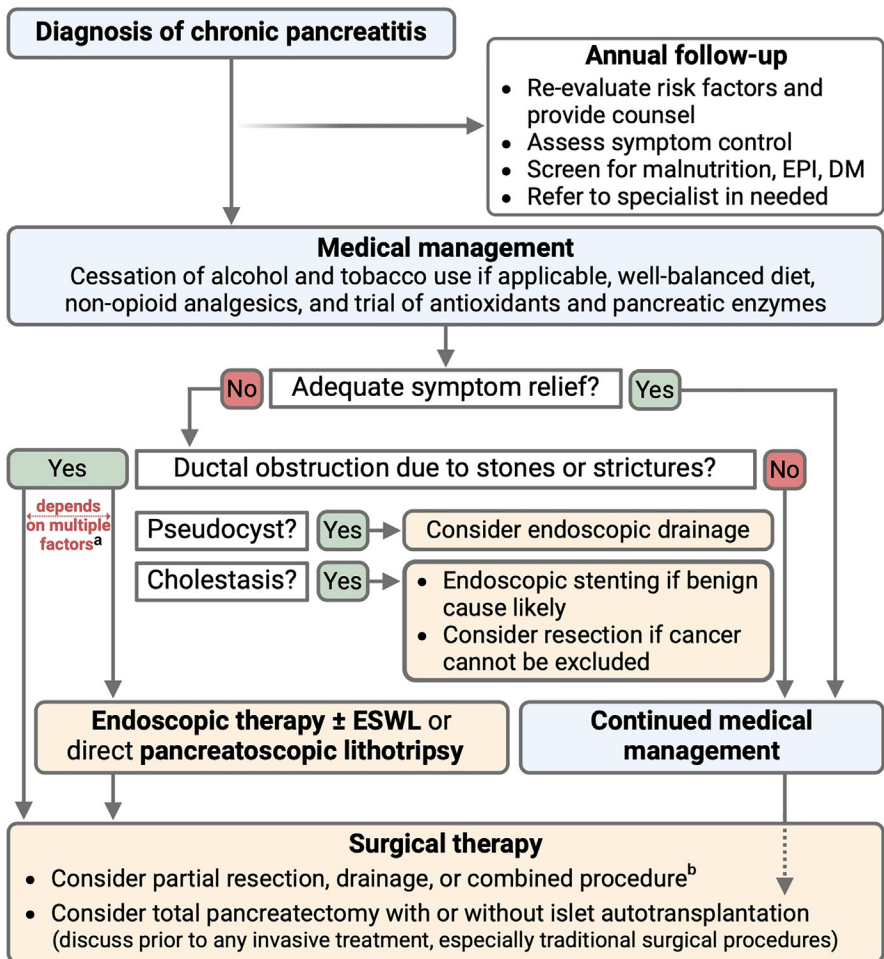
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endoscopy, surgery, and psychological care.<sup>2,5,6</sup> Key areas of focus include addressing abdominal pain, exocrine and endocrine insufficiencies, structural complications, and enhancing quality of life (QoL; Fig. 1).

### Pain Management

Pain is the predominant symptom and leading cause of hospitalization, disability, as well as unemployment among patients with CP.<sup>1</sup> Mechanisms of CP pain are multiple, including pancreatic duct obstruction, secondary biliary and duodenal obstruction, pancreatic inflammation, ischemia, pseudocysts, and increasingly, local neural inflammation and central sensitization.<sup>7</sup> CP pain pattern and severity are independent of structural findings on cross-sectional imaging.<sup>8</sup> Seventy-five percent of patients report pain



**Fig. 1.** Suggested algorithm for management of chronic pancreatitis. <sup>a</sup>The choice between an endoscopic or surgical procedure as the initial approach depends on multiple factors (see text). <sup>b</sup>Partial resections or drainage has no role in patients without obstructive disease. DM, diabetes mellitus; EPI, exocrine pancreatic insufficiency; ESWL, extracorporeal shockwave lithotripsy.

at disease presentation and nearly 100% as time progresses.<sup>9</sup> Each underlying mechanism of CP pain requires individual management.<sup>10,11</sup> Given that pathophysiology, assessment, and management of CP-associated pain are addressed in a separate article within this journal issue, we avoid delving into details to prevent redundancy.

Pain patterns can be categorized into 5 types<sup>3,12</sup>: type A (intermittent episodes of mild/moderate pain—but no constant pain), type B (constant mild/moderate pain—but no attacks of pain), type C (episodes of severe pain—but no constant pain), type D (constant mild/moderate pain AND episodes of more severe pain), and type E (constant, severe pain). Treatments may vary with different pain pattern.

All patients with painful CP should be strongly encouraged and supported to stop drinking alcohol and smoking. Additionally, optimizing pancreatic enzyme replacement therapy (PERT) and nutritional therapy is crucial to prevent malnutrition, even though direct alleviation of pain is debated.<sup>2,11,13</sup> However, some reports indicate that pain may be reduced by PERT even in normal pancreatic function, especially using non enteric-coated enzyme formulations.<sup>10,14</sup>

For mild abdominal pain or pain without significant duct obstruction, initial treatment should be medical, following the World Health Organization pain relief ladder.<sup>10,15</sup> Medical therapy is recommended to be integrated with psychological interventions for reduced QoL due to pain.<sup>10</sup> To identify the most appropriate strategy, patients should undergo an early evaluation by an interdisciplinary team soon after the onset of CP.<sup>11</sup>

Approximately 30% to 60% of patients who have persistent pain despite medical treatment require invasive interventions such as endoscopic procedures or surgery.<sup>16</sup> Major traditionally recognized and anatomically intervenable causes of persistent pain are main pancreatic duct (MPD) obstructions due to stones or strictures, biliary obstructions, and the presence of pseudocysts.<sup>10,11,17</sup> Increasingly, local inflammation, neuropathic pain, and other nonobstructive factors are thought to contribute to pain that can respond to total pancreatectomy, despite the absence of obvious morphologic changes.<sup>18–20</sup>

Celiac plexus block is a minimally invasive, non-narcotic means of alleviating pain of pancreatic and retroperitoneal origin. Evidence shows it reduces pain in 50% of patients with CP, but the effect is temporary, lasting only weeks to months.<sup>21</sup> Endoscopic ultrasound (EUS)-guided celiac plexus block may be considered after exhausting medical options, mainly if the intent is for short-term pain reduction. Repetitive celiac blocks are resource intensive and may lead to complications. As such, other methods should be adopted before disease progression.

### ***Nutritional Management and Pancreatic Enzyme Replacement Therapy***

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Nutritional assessments and counseling are vital for patients with CP, despite the absence of a gold standard for screening.<sup>4,5</sup> A large randomized controlled trial (RCT) demonstrated that nutritional evaluation and treatment reduced morbidity and mortality in non-critically ill inpatients.<sup>22</sup> Clinical tools such as the Nutritional Risk Screening 2002 and selected laboratory parameters are integral.<sup>23</sup> While no specific CP diet has proven superior to a balanced diet, physicians should be aware of the increased risk of osteoporosis.<sup>24</sup> Patients should be screened for micronutrient and macronutrient deficiencies at least annually, with more frequent assessments for those with severe disease or uncontrolled malabsorption.<sup>25</sup> Monitoring should include fat-soluble (A, D, E, K) and water-soluble (vitamin B12, folic acid, thiamine) vitamins, as well as minerals such as magnesium, iron, selenium, and zinc should be monitored. Supplementation is recommended for patients with known malabsorption or detected deficiencies.<sup>25</sup>

Importantly, assessing the nutritional status of patients with CP requires a comprehensive approach beyond mere evaluation of body mass index. Recent research highlights the importance of assessing sarcopenia, a condition characterized by loss of muscle mass and function, which is common among patients with CP.<sup>26,27</sup> In fact, over half of patients with CP were found to be overweight or obese, yet they had lower muscle stores and reduced functional status, as measured by hand grip strength, compared to controls.<sup>26</sup> Moreover, sarcopenia in patients with CP has been associated with increased hospitalization rates and reduced survival, emphasizing the critical impact of muscle health on patient outcomes.<sup>27</sup> In addition to hand grip strength, other easily accessible methods to assess sarcopenia include measuring muscle mass through bioelectrical impedance analysis or dual-energy x-ray absorptiometry (DEXA). Functional assessments such as gait speed and chair stand tests can also provide valuable insights into the patient's physical capabilities.

CP-related malnutrition is caused by concurrent exocrine pancreatic insufficiency (EPI) and postprandial abdominal pain. A long-term follow-up study indicated that EPI was a significant independent risk factor for mortality (hazard ratio 2.59, 95% confidence interval [CI] 1.42–4.71).<sup>28</sup> Additionally, a recent meta-analysis found that PERT reduces symptoms and enhances nutritional status.<sup>29</sup> All patients with EPI, and those showing signs of malnutrition, should receive 40,000 to 50,000 lipase units per meal.<sup>11,30</sup> The dosage should be increased until symptoms are alleviated. Monitoring for treatment effectiveness includes tracking improvements in steatorrhea, weight gain, levels of fat-soluble vitamins, and measurements of bone density and muscle mass. For those who do not respond to treatment, an indirect pancreatic function test can be conducted. If necessary, proton pump inhibitors can be used to enhance the treatment's effectiveness, especially with non enteric-coated formulations. Notably, dietary fat restriction should be avoided to prevent unwanted weight loss and deficiencies in fat-soluble vitamins and essential fatty acids.<sup>25</sup>

### **Management of Bone Disease**

Patients with CP are at a significant risk for bone disease.<sup>31</sup> A systematic review and meta-analysis found a pooled prevalence rate of osteoporosis to be 24.3% (95% CI 16.6%–32.0%) and osteopathy (either osteoporosis or osteopenia) to be 65% (95% CI 54.7%–74.0%).<sup>32</sup> Data suggest that vitamin D deficiency is not the only factor contributing to bone demineralization in CP. Other important contributors to premature bone demineralization include heavy smoking, low physical activity, and chronic inflammation.<sup>31,33</sup>

Basic preventive measures should be advised to all patients with CP to reduce the risk of bone disease.<sup>31,34</sup> These include ensuring adequate intake of calcium and vitamin D, with supplements provided if dietary intake is insufficient. For patients with malabsorption, PERT can enhance nutrient absorption, including essential vitamins and minerals. Furthermore, regular weight-bearing exercises, such as walking, jogging, and resistance training, are crucial for maintaining bone density. Pharmacologic treatment should be reserved for patients with proven osteopathy and, in particular, osteoporosis.<sup>31</sup>

DEXA is the recommended diagnostic tool for identifying bone disease in patients with CP, capable of detecting both osteoporosis and osteopenia.<sup>31,34</sup> Nevertheless, the specific timing and target population for testing among patients with CP are not yet well defined.<sup>31</sup> The American Gastroenterological Association guidelines on osteoporosis in gastrointestinal diseases recommends that patients with inflammatory bowel disease, celiac disease, and post-gastrectomy should undergo DEXA if they have at least one additional osteoporosis risk factor.<sup>35</sup> The HaPanEU guidelines

proposed that bone density testing using DEXA should be extended to CP patients with additional risk factors, such as post-menopausal women, individuals with previous low-trauma fractures, men aged over 50 years, and those with malabsorption.<sup>34</sup> Moreover, they suggested that, given the morbidity and costs associated with bone fractures, it may be beneficial to conduct a baseline bone density assessment for all patients with CP. If bone pathology is confirmed, DEXA should be repeated every 2 years.<sup>34,35</sup>

### **Endocrine Insufficiency Treatment**

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Endocrine insufficiency can also be a consequence of CP, known as diabetes of the exocrine pancreas or type 3c diabetes mellitus (T3cDM). It is estimated to affect 25% to 80% of patients with CP, typically emerging 10 to 20 years after the initial diagnosis.<sup>11</sup> Notably, newly diagnosed diabetes may be an early sign of pancreatic cancer and warrants further assessment in all patients with CP.<sup>36</sup>

Managing T3cDM aligns with general diabetic guidelines. The medical management should be always paired with a healthy lifestyle, including routine exercise and a balanced diet. Optimizing PERT enhances duodenal sensing and the absorption of complex nutrients, helping to stabilize blood sugar levels.<sup>11,13</sup> Pancreatogenic diabetes poses an increased risk of hypoglycemia due to impaired counter-regulation, so proper counseling is essential. Insulin therapy is often preferred, but metformin is also recommended for mild hyperglycemia (HbA1c <8%). Besides its glucose-lowering benefits, a meta-analysis of 12 observational studies also indicated that metformin reduces the risk of pancreatic cancer in patients with diabetes (summary risk ratio 0.73, 95% CI 0.56–0.96).<sup>37</sup>

### **Interventional Therapy**

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Endoscopic therapy is often the first intervention for moderate-to-severe *pancreatic pain* that does not respond to medical therapy.<sup>38</sup> It mainly involves the removal of stones and dilatation of strictures within the MPD. Extracorporeal shockwave lithotripsy (ESWL) may be used for stone fragmentation, either alone or alongside endoscopic retrograde cholangiopancreatography (ERCP).<sup>39,40</sup> Increasingly, per-oral pancreatoscopy with intraductal lithotripsy using electrohydraulic or laser lithotripsy have been shown to provide expeditious and total duct clearance for MPD stones.<sup>41–43</sup> For MPD strictures, prolonged dilatation with multiple small-caliber plastic stents or a single 10 Fr plastic stent, with intermittent stent exchanges as needed, is typically necessary, providing pain relief in over 70% of patients.<sup>38</sup> Endoscopic management is also utilized for complications of CP, such as pancreatic duct leaks, pseudocysts and pancreatic ascites. Traditional surgical options for pain relief include drainage procedures for ductal obstruction (ie, longitudinal pancreaticojejunostomy and its variants), resection for persistent focal inflammation (ie, standard pancreaticoduodenectomy and its variants or distal pancreatectomy), or a combination (eg, Frey or Izbicky procedures).<sup>44–46</sup> When it comes to resection, surgeons often prefer the Frey procedure or other duodenum-preserving techniques to maintain the critical structural and enteroendocrine functions of the duodenum. Nevertheless, a recent European multicenter trial comparing QoL 2 years postoperatively in patients randomized to partial pancreaticoduodenectomy and duodenum-preserving pancreatic head resection found no significant difference in QoL outcomes or adverse events between the two groups.<sup>47</sup> Notably, optimal outcomes are achieved when surgery is performed before opioid dependence and neuropathic pain develop.<sup>34,46,48</sup>

There is an ongoing debate whether surgical or endoscopic therapy should be the initial treatment. Most of the debates have centered around studies that are two or

more decades old and thus do not reflect either the current state of the art with respect to endoscopic therapy or incorporate newer advances in surgery. These studies included only surgically fit patients with dilated MPD, a combination which is frequently absent in the full spectrum of patients with CP. Three RCTs compared surgery to endoscopic therapy for painful CP, revealing higher pain relief rates with surgery (34%–78%) compared to endoscopy (15%–39%).<sup>45,49,50</sup> Both approaches had similar adverse event rates and mortality, but endoscopy required more reinterventions. The most recent ESCAPE trial, published in 2020, included 88 patients and compared best medical management with endoscopic treatment versus upfront early surgery for painful CP.<sup>45</sup> An important finding was that complete endoscopic duct clearance of stones resulted in similar pain improvement between treatment groups. In this study, ESWL combined with conventional endoscopic therapy was the only option. Using those techniques, only 62% of patients in the endoscopy group achieved complete clearance. As commented by the authors of the ESCAPE trial, direct per-oral pancreatoscopy with intraductal electrohydraulic or laser lithotripsy has been widely utilized in the last decade and allows complete duct clearance in a greater proportion of patients, and it may have already changed the landscape of potential therapies.

Given that endoscopic therapy is less invasive and does not preclude later surgery, it is typically preferred initially by both physicians and patients. The choice is also based on surgical candidacy, pancreatic duct anatomy, stone burden, endoscopic accessibility through the downstream duct, and distribution of the disease within the gland. Endoscopic therapy may be beneficial with symptomatic duct obstruction in the head or neck of the pancreas, accompanied by upstream duct dilatation, and in patients with small duct disease with stones or strictures. In contrast, patients with a large inflammatory mass in the pancreatic head, downstream pancreatic stenosis, and mass-like calcifications of the pancreatic head side branches can be difficult to treat endoscopically.<sup>16</sup> In both scenarios, the use of multiple plastic stents or possibly fully covered self-expandable metal stents, with concern about occlusion of the side branches, have been effective for relieving pancreatic outflow obstruction. Novel approaches include the use of biodegradable stents.<sup>51–53</sup>

Surgery should be considered early, and not infrequently as first-line therapy, without resorting to endoscopic therapy in good surgical candidates where either endoscopic therapy is likely to fail, or patients will have difficulty complying with repeat procedures. Otherwise, when endotherapy does not provide immediate symptom relief, the timing of surgical therapy may be an important factor for optimal long-term pain relief.<sup>5</sup> The outcomes of conventional drainage or resection surgery are better when patients are referred within 3 to 5 years of symptom onset and have had fewer than 4 endoscopic interventions.<sup>5,11</sup> The choice of surgical technique depends on several factors, including the patient's anatomy, disease course, and local preferences.<sup>54</sup> Laparoscopic and robotic surgeries are becoming increasingly popular, being utilized for various pancreatic resections, drainage procedures, and even total pancreatectomies.<sup>55</sup> It must be kept in mind that in the entire spectrum of patients with CP, only a minority have suitable anatomy for conventional surgical approaches—those with large duct disease, and absence of associated comorbidity such as portal hypertension, cardiopulmonary disease, or other factors that render them unsuitable for a major abdominal operation. In addition, over the long term, at least 50% of patients undergoing conventional drainage operations have persistent or recurrent pain.<sup>49,56,57</sup>

Total pancreatectomy with islet autotransplantation (TPIAT) is an increasingly available option, first reported in 1977 at the University of Minnesota.<sup>58,59</sup> The procedure involves complete pancreaticoduodenectomy and splenectomy, with removal of the source of pain, while attenuating or preventing diabetes by reimplanting the patient's

own islet cells into the portal circulation or peritoneal cavity.<sup>44,60</sup> Its goals are to alleviate chronic pain and disability through total pancreatectomy, while minimizing or preventing postsurgical diabetes. TPIAT is an ideal option for younger patients with progressive hereditary disease, patients with small duct disease, and those refractory to conventional therapies who do not have diabetes or major comorbidity.<sup>59,61–64</sup> Most patients experience pain improvement (85%) and cessation of opioid use (59%) post-TPIAT, with durable results as 82% maintain pain relief at 10 years.<sup>61,65</sup> QoL is significantly improved by islet function more than 10 years after TPIAT, compared with patients without islet function.<sup>20</sup> As in all interventions for CP, a minority of patients still experience significant pain postoperatively, potentially due to factors like central sensitization and gastrointestinal dysmotility.<sup>60,66</sup> Notably, outcomes are best in younger patients and children.<sup>67</sup> The outcomes of TPIAT in a prospective, multicenter, NIH-funded study are currently undergoing analysis, and will shed important light on outcomes and predictors.<sup>59</sup>

For *pancreatic duct stones*, the European Society of Gastrointestinal Endoscopy recommends endoscopic therapy as first-line treatment.<sup>38</sup> Endoscopic extraction, with or without protective stenting, remains the preferred treatment particularly for stones located in the head or neck of the pancreas and when there are fewer stones, although multiple stones can now be readily addressed with intraductal pancreatoscopic lithotripsy techniques. Conversely, surgery is recommended for more distal (upstream) stones and in cases with prevalent local complications.<sup>16,50,56</sup> ESWL can also be offered for stones not likely amenable to conventional endoscopic techniques.<sup>38</sup> According to a nationwide survey from Japan, endoscopy alone facilitated stone extraction in only a minority of patients (14% of 1,834 cases),<sup>68</sup> although such is not the experience in most Western countries. On the other hand, ESWL allowed stone extraction in more than 80% of patients on subsequent endoscopy.<sup>69</sup> Pancreatic duct stone fragmentation was shown to be successfully achieved in up to 90% of patients following ESWL, although multiple sessions may be required, as each treatment focuses on a limited area.<sup>70,71</sup> Notably, the first recently completed RCT comparing combined ESWL and ERCP with sham procedures in patients with intraductal stones demonstrated a modest reduction in pain among the ESWL/ERCP group compared with the sham group.<sup>72</sup> This improvement was accompanied by a decrease in the use of opioid-based analgesics and an overall better-perceived health status after a 12 week follow-up. However, the difference was not sustained at the 24 week follow-up. These results are difficult to integrate with other studies such as the ESCAPE trial.

Through-the-scope mechanical lithotripsy may be used to fracture and extract pancreatic duct stones that cannot be removed by conventional techniques.<sup>73</sup> However, a retrospective study of 712 patients found it was associated with higher rates of adverse events, such as fractured traction wire, trapped basket, or ductal leak.<sup>74</sup> Pancreatoscopy-guided lithotripsy has been introduced as an alternative, as it can facilitate direct lithotripsy with less resource-intensive equipment compared to ESWL (Fig. 2). A recent meta-analysis comprising 15 studies and including 370 patients with pancreatic duct stones treated with either electrohydraulic or laser lithotripsy found both techniques to have similar efficacy; technical and clinical success rates were approximately 90%.<sup>41</sup> Furthermore, a recent multicenter retrospective study reported pancreatoscopy-guided lithotripsy advantageous compared to ESWL due to the need for fewer sessions to achieve pancreatic stone clearance.<sup>43</sup>

*Pancreatic fluid collections* and *pseudocysts* need treatment only if symptomatic.<sup>34</sup> EUS-guided transmural drainage is the treatment of choice, with double-pigtail plastic stents usually sufficient for clinical success.<sup>38</sup> Small collections are often optimally



**Fig. 2.** Per oral pancreatoscopy showing pancreatic stone fragmentation using electrohydraulic lithotripsy under direct vision.

treated with transpapillary stenting to address a duct leak, or occasionally by a combination of EUS-guided aspiration plus transpapillary pancreatic stent to bridge the leak. Alternatively, transmural lumen-apposing metal stents are used.<sup>75</sup> Plastic stents should remain for at least 3 months to prevent recurrence, while metal stents need earlier removal or replacement with plastic stents to avoid migration and bleeding due to erosion into vessels, especially after drainage of predominantly fluid collections.<sup>76–78</sup> Surgical internal drainage is an option in endoscopic failure.<sup>16</sup> In cases of known pancreatic duct disruption or recurrent pancreatitis, additional transpapillary stenting is recommended; otherwise, dual stenting appears to offer no added benefit.<sup>79–81</sup>

Impaired MPD drainage either from a *pancreatic duct stricture*, stenosed pancreaticoenteral tract anastomosis after a pancreateoduodenectomy, or in patients with *disconnected pancreatic duct syndrome* after necrotizing pancreatitis may cause recurrent acute pancreatitis or CP in the upstream pancreas.<sup>81–84</sup> Surgical pancreaticojejunostomy is often not feasible in patients with small ducts, and surgical resection of the upstream gland can lead to diabetes and generally requires splenectomy.<sup>85,86</sup> Endoscopic pancreatic ductal drainage emerged as an alternative, particularly for those deemed poor candidates for surgery. Transpapillary pancreatic endotherapy performed via ERCP is only an option for strictures with a partially connected MPD.<sup>87–89</sup> It may be unfeasible in 3% to 10% of cases,<sup>90</sup> mainly due to very tight strictures, complete obstruction, altered anatomy, or a disconnected duct.<sup>80,81,91–94</sup> Interventional EUS, on the other hand, allows transluminal access to and drainage of the MPD using various approaches.<sup>95–97</sup>

EUS-guided pancreatic drainage, first introduced by Francois and colleagues in 2002<sup>95</sup> and its rendezvous variant by Mallery and colleagues in 2004,<sup>97</sup> has been successfully employed for MPD decompression in patients with both native and surgically altered anatomy.<sup>94,98,99</sup> Most studies have focused on patients with a dilated MPD, which occur inconsistently in obstructive CP, and used more or less invasive techniques for duct access, such as electrocautery, bougie, screw dilation, and angioplasty balloons. However, there are also reports of successful use of EUS-guided

pancreaticogastrostomy in patients with small-caliber pancreatic ducts utilizing a less invasive approach.<sup>100</sup>

*Biliary stricture* occurs in 10% to 15% of patients with CP, and the primary concern is to exclude malignancy. Once malignancy is ruled out, the stricture can be treated with endoscopic, surgical, or interventional radiologic techniques. RCTs indicate that endoscopic treatment is reliable.<sup>101,102</sup> Furthermore, a recent meta-analysis involving 1,298 patients with benign common bile duct stenosis (including patients with CP) treated with covered self-expandable metal stents demonstrated excellent long-term outcomes, with stenosis resolution in 83% (95% CI 78%–87%).<sup>103</sup> Additionally, multistenting using plastic stents is equally effective as metal stents but is more time-consuming.<sup>101</sup>

Finally, CP can lead to *vascular complications*, such as pseudoaneurysms in adjacent arteries, especially the splenic artery, or venous thrombosis. A meta-analysis of 29 studies involving 849 patients with pseudoaneurysms reported an 88% clinical success rate for endovascular embolization at 12 months.<sup>104</sup> Splenic vein thrombosis is typically managed expectantly, but a meta-analysis found left-sided portal hypertension causing gastric bleeding in up to 12.3% of cases.<sup>105</sup> For these, splenic artery embolization can serve as a therapeutic option, while splenectomy is a definitive solution.

### **Emerging Therapies**

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Recent advancements in treatment focus on novel therapeutic targets, including anti-inflammatory agents and regenerative medicine. As of now, there is no curative medical therapy for CP. However, research into the mechanisms of CP is uncovering potential therapeutic avenues, which are being tested in human clinical trials after showing promise in animal models. For instance, inhibiting the effects of interleukins 4 and 13 has been demonstrated effective to reduce CP.<sup>106</sup> Another example is pirfenidone, an Food Drug and Administration-approved agent for treating idiopathic pulmonary fibrosis by inhibiting TGF- $\beta$  actions to promote fibrosis; it has also shown benefits in CP models.<sup>107</sup> Simvastatin, which has the potential for the use in CP by inhibiting the inflammatory response through correcting autophagic mechanisms in disordered acinar cells, is currently in clinical trials (NCT04021498, NCT02743364).<sup>108,109</sup> A highly potent vitamin D analog paricalcitol, which returns activated pancreatic stellate cells to their quiescent state, is also in an early trial (NCT05664880) as a potential treatment for CP.<sup>110</sup> Finally, immune-modulating therapies for sterile inflammation have been approved, and computer modeling suggests similar treatments might be beneficial in the case of CP.<sup>111</sup>

A recent study comparing gut microbiota in TPIAT candidates and healthy controls indicated that changes in gut microbial community structure may contribute to gastrointestinal symptoms and thus provided potential basis for future studies on whether enrichment of healthy commensal bacteria could provide clinically meaningful improvements in outcomes for patients with CP undergoing TPIAT.<sup>112</sup>

### **Psychological Support**

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Psychological therapy is pivotal in a multidisciplinary care model for chronic pain, given the high prevalence of depression and anxiety among suffering patients.<sup>6</sup> Incorporating psychological therapy into CP management can enhance patient outcomes by addressing the complex interplay between pain, mental health, and overall QoL.<sup>6,113</sup> Cognitive behavioral therapy (CBT), stress management and resilience training, specialized pain rehabilitation programs, and addressing nicotine, alcohol, and narcotic addictions are key additions to structural interventions.<sup>114</sup>

CBT helps patients reframe maladaptive thoughts about their pain, thus improving their coping mechanisms and reducing pain-related anxiety. Additionally, mindfulness

and acceptance-based therapies help manage chronic pain by focusing on present-moment experiences and reducing its emotional impact.<sup>115,116</sup> Despite CBT's effectiveness in related contexts,<sup>117</sup> evidence for psychological interventions in treating chronic pain in CP patients remains limited.<sup>6</sup> Nonetheless, the feasibility and preliminary efficacy of CBT pain self-management has been demonstrated in a recent RCT.<sup>118</sup> Sixty adults with suspected or definite CP were studied; 30 participants received Internet-based CBT consisting of 5 sessions over 8 weeks, while the rest served as controls. Pain interference, intensity, and QoL were measured before treatment, after treatment, and at 3 month follow-up. The Internet-based CBT group had a significantly higher percentage of patients with over 30% improvement compared to the control group (50% vs 13%,  $P=.04$ ).

Furthermore, psychological therapies are crucial for managing comorbid psychiatric conditions and promoting treatment adherence.<sup>119</sup> Psychologists educate patients on the biopsychosocial aspects of CP, screen for substance abuse and suicidal ideation, and optimize physical and mental health outcomes.<sup>6,120</sup>

### ***Treatment Response Assessment and Prediction***

Evaluating and predicting treatment efficacy is difficult in CP, and it is a subject of rigorous research. A University of Pittsburgh-based trial (NCT04996628) investigates the ability of Pancreatic Quantitative Sensory Testing to predict responses to invasive treatments in painful CP and aims to develop a predictive model for individualized treatment outcomes. The QOLAPI (NCT03632616) and EQuIPP (NCT05012150) trials are currently enrolling participants to assess the impact of endoscopic management on pain, QoL, and pancreatic functions. Additionally, the Dutch Pancreatitis Study Group is conducting the COMBO trial (ISRCTN13042622), a stepped-wedge cluster-RCT involving 26 centers, which uses an evidence-based management algorithm to evaluate the impact of an integrated therapeutic approach on QoL and pain intensity relative to traditional treatments.<sup>121</sup> This study, including 1165 patients with CP, has identified nutritional status, pancreatic exocrine function, employment status, and coping strategies as critical and influential factors in enhancing QoL.<sup>122</sup> Additionally, the Chronic Pancreatitis Prognosis Score, a dynamic multivariate scoring system, has been developed to assess the risk of hospitalization and readmission in patients with CP.<sup>123</sup>

### **SUMMARY**

Managing CP necessitates an interdisciplinary approach, and patients should have at least annual evaluations to assess causal risk factors, symptom control, and disease-related complications. Importantly, referral to a specialized center is advised if symptoms are poorly controlled or there is a risk of deterioration.

Interventional endoscopy and surgery offer effective and long-lasting symptomatic treatment of selected patients and should be performed by specialists, with early treatment discussions involving all relevant medical disciplines. Currently, there is no curative medical therapy for CP, and TPIAT offers the only "ultimate" solution, although novel therapeutic avenues involving causative treatments are being investigated.

### **CLINICS CARE POINTS**

- Treatment starts with alcohol and smoking cessation, along with optimizing nutrition. Exocrine insufficiency results in weight loss, sarcopenia, and deficiencies in fat-soluble

vitamins and other micronutrients and is mitigated by treatment with pancreatic enzyme supplementation.

- Interdisciplinary approach that integrates behavioral pain management, psychiatric evaluation and treatment of depression, anxiety, and addiction, alongside medical and surgical management, proves to be more effective and lowers overall health care costs.<sup>113</sup>
- Interventional treatment is indicated in refractory abdominal pain unresponsive to medical therapy, presence of MPD stones, symptomatic or refractory MPD strictures, or local complications, such as common bile duct stenosis or duodenal stenosis.<sup>38</sup>
- Traditional drainage surgery may offer better long-term outcomes compared to traditional endoscopic methods, but both surgical and endoscopic approaches have evolved substantially in recent years. In centers with appropriate multidisciplinary expertise, less invasive options including ERCP and/or EUS-guided interventions may be either preferable or the only feasible options in patients without optimal large duct anatomy or suitable comorbidity profile for surgical drainage or resection.
- Total pancreatectomy with or without islet autotransplantation should be considered in selected cases, particularly younger patients with genetic or idiopathic etiology. Discussion about pancreatectomy with or without islet autotransplantation should occur before any invasive treatment, especially before traditional surgical procedures, as they impair islet yield.

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## DISCLOSURES

The authors have nothing to disclose.

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