ACG Clinical Guideline: Chronic Pancreatitis

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Chronic pancreatitis (CP) is historically defined as an irreversible inflammatory condition of the pancreas leading to varying degrees of exocrine and endocrine dysfunction. Recently however, the paradigm for the diagnosis has changed in that it breaks with the traditional clinicopathologic-based definition of disease, focusing instead on diagnosing the underlying pathologic process early in the disease course and managing the syndrome more holistically to change the natural course of disease and minimize adverse disease effects. Currently, the most accepted mechanistically derived definition of CP is a pathologic fibroinflammatory syndrome of the pancreas in individuals with genetic, environmental, and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress. The most common symptom of CP is abdominal pain, with other symptoms such as exocrine pancreatic insufficiency and diabetes developing at highly variable rates. CP is most commonly caused by toxins such as alcohol or tobacco use, genetic polymorphisms, and recurrent attacks of acute pancreatitis, although no history of acute pancreatitis is seen in many patients. Diagnosis is made usually on cross-sectional imaging, with modalities such as endoscopic ultrasonography and pancreatic function tests playing a secondary role. Total pancreatectomy represents the only known cure for CP, although difficulty in patient selection and the complications inherent to this intervention make it usually an unattractive option. This guideline will provide an evidence-based practical approach to the diagnosis and management of CP for the general gastroenterologist.

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INTRODUCTION

Recent advances in clinical and translational sciences continue to alter our understanding of chronic pancreatitis (CP) and are forcing changes in the definition, diagnosis, and management approaches. The emerging paradigm, which breaks with the traditional clinicopathologic-based definition of disease, focuses on diagnosing the mechanistic disorder underlying the pathogenic process early in the disease course and managing the syndrome more holistically to change the natural course of disease and minimize adverse disease effects (1). This new paradigm falls into the realm of precision medicine for complex disorders, a "bottom-up" approach focusing on complex gene and environmental interactions in an individual patient with early signs and symptoms of disease (2). For complex disorders with multiple etiologies, modifiers, complications, and outcomes, a precision medicine approach is required.

Before 2016, CP was defined using a traditional clinicopathologic approach with typical signs and symptoms linked to defined pathology—i.e., chronic inflammation and irreversible fibrosis without infection. The primary challenge was in obtaining pancreatic tissue, the "gold standard" for a pathologic diagnosis, especially in the setting of the high risk/benefit ratio linked with biopsies. Three consensus conferences in Marseille, France, between 1963 and 1989 defined CP on the basis of clinical, functional, and histologic evidence (3–5). In 1984, the "Cambridge definition" was proposed as a clinically useful alternative to biopsy by using an endoscopic retrograde cholangiopancreatography (ERCP) scoring system as a surrogate for tissue (6). CP was defined as *a continuing inflammatory disease of the pancreas, characterized by irreversible morphological change, and typically causing pain and/or permanent loss of function*. This definition served as the basis for imaging approaches to the diagnosis of CP (in the context of typical symptoms and loss of function) and the foundation for most consensus statements and clinical guidelines for the next 3 decades.

The Cambridge definition and score served to significantly advance the field, but the traditional clinicopathologic definition of disease and research approaches based on Koch's postulates failed to provide insights into the complex causes and care of individual patients or significantly change the natural history of the disease (7,8). Furthermore, new technologies and discoveries over the 35 years between 1984 and 2019 proved that new data cannot be used within the old clinicopathologic paradigm. Early CP, the stage in which targeted therapy is likely to be most effective, cannot be diagnosed using the clinicopathologic definition of CP because it requires the presence of *irreversible morphologic change* (9). In the case of early CP, increasing imaging sensitivity is

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associated with decreasing specificity. Furthermore, examination of the pathology, or images as a surrogate, offers little insight into any of the dozens of potential underlying simple or complex etiologies. Genetics clearly play a major role in pancreatic diseases, but because germline variants rarely link to specific symptoms or tissue pathologic features, they cannot be understood within the clinicopathologic framework. It follows that clinical genetic reports that are framed by classic Mendelian geneticists or anatomic pathologists within the clinicopathologic framework provide little clinical guidance, especially in the later stages of disease. In addition, the practice of diagnosing and tracking disease progression based on fibrosis may be flawed because the degree of fibrosis correlates poorly with pain, exocrine pancreatic insufficiency (EPI), diabetes mellitus (DM), progressive disease, or cancer risk—the primary concerns of clinical care (10–14).

In summary, the traditional clinicopathologic framework that defines the CP syndrome by irreversible damage results in years of delay between symptom onset and diagnosis and usually fails to identify or address the underlying etiology, cannot predict the clinical course, cannot direct preventative treatments that change disease trajectory, and remains limited to symptomatic or supportive care and replacement of lost gland function.

In 2016, a new Mechanistic Definition of CP was published, and later adopted, by the major pancreas societies as the preferred definition worldwide (15,16). The Mechanistic Definition affirms the characteristics of end-stage disease as *pancreatic atrophy, fibrosis, pain syndromes, duct distortion and strictures, calcifications, pancreatic exocrine dysfunction, pancreatic endocrine dysfunction, and dysplasia*, but also addresses the disease mechanism as *a pathologic fibroinflammatory syndrome of the pancreas in individuals with genetic, environmental, and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress*. The definition is linked to a progressive model to organize risk factors, clinical scenarios, disease biomarkers, sequential and progressive features, and individual variables within a lifetime. It was also designed to assess the differential diagnosis of disorders with pathologic features that overlap with early CP, such as fibrosis, atrophy, maldigestion, and diabetes.

Within the framework of the Mechanistic Definition, it is important to recognize the difference between *pancreatic dysfunction*, *pancreatitis-related disorders*, and *pancreatic disease*. The term *dysfunction* is a dynamic term that describes a variation in the action of an entity that deviates from normal in a negative way. A *medical disorder* indicates disruption of the normal functions of specialized cells or systems resulting in abnormal signs, symptoms, biomarkers, and/or responses. A *disease* is an abnormal condition in a living animal that is defined by consensus criteria consisting of abnormal signs and symptoms, abnormal biomarkers, and typical pathologic features.

An example of *pancreatic dysfunction* is the presence of a genetic mutation in the *CFTR* gene locus that causing variations in RNA expression or splicing, or changes in amino acid sequence causing defective processing, trafficking, or channel opening. The dysfunction may be tolerated by adaptive mechanisms and limited cell stress so that the cells using CFTR do not fail under most conditions. An example of a *pancreatitis-related disorder* would be protein dysfunction that causes the pancreatic duct cell to fail to respond normally when the cell is strongly stimulated or stressed, resulting in a duct cell dysfunction. When the compensatory threshold is exceeded, then internal and external stress and injury signals are generated that may cause clinical signs and symptoms of diseases, such as an episode of acute pancreatitis (17). *Pancreatic diseases* are conditions that are typically associated with pathology such as acute pancreatitis, recurrent acute pancreatitis (RAP), CP, and complex syndromes that affect the pancreas such as cystic fibrosis. When the clinical evaluation of the patient determines the presence of clinical, functional, and morphologic features that meet consensus criteria, then the patient may be diagnosed as having a disease, such as CP. If multiple organs are involved, then the patient is diagnosed with a genetic disease, such as *cystic fibrosis* with pancreatic sufficiency or insufficiency. Precision medicine therefore focuses on determining the dysfunction and the disorder and seeks to use targeted therapy to prevent the condition from progressing to a clinicopathologic-defined disease. However, new studies are needed to evaluate the effectiveness of targeted therapies in individual patients (2,18). At this time, a paucity of studies exists specifically using the new Mechanistic Definition of CP.

In this context, a group of experts within the ACG were tasked to complete a systematic review of the literature concerning CP and develop guidelines for the membership. Based on the framework of the traditional definition and approaches to CP, much of the older literature provides limited insights and context for strong recommendations. The authors expect, moving forward, that future guidelines will be more reliant on studies executed under the framework of the Mechanistic Definition of CP. Where possible, specific clinical questions are poised, followed by a review and recommendations based on the older literature and comments on future directions.

METHODOLOGY

With the assistance of a health science librarian, a literature search was completed through MEDLINE (1946-current), Embase (1974-current), Web of Science (1900-current), and the Cochrane Library. All databases were searched up to February 2018. The search strategy MeSH terms included chronic pancreatitis or pancreatitis (chronic or minimal change). Searches were limited to the English language. Two authors (T.B.G. and J.R.T.) independently reviewed all unique articles and included those articles that met consensus criteria. The authors also incorporated articles from review of references in retrieved manuscripts as well as relevant studies known to the authors. The search results were primarily randomized trials. If these were not available, then meta-analyses and systematic reviews were used.

The guideline is structured in sections, each with recommendations or key concepts, and summaries of the evidence based on the PICO question format that is a consistent "formula" for developing answerable, researchable questions. PICO is an acronym that includes the following 4 aspects important for research questions: 1. population/problem, 2. intervention, 3. comparison, and 4. outcome. The PICO questions were developed by the consensus of the authors and served as the basis for each recommendation and key concept (Table 1). Each recommendation statement has an associated assessment of the quality of evidence and strength of recommendation based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process. The GRADE system was used to evaluate the quality of supporting evidence. A "Strong" recommendation is made when the benefits clearly outweigh the negatives and/or the result of no action. "Conditional" is used when some uncertainty remains about the balance of benefits and potential harms. Statements with a "strong" recommendation are stated with "We recommend," whereas statements with

Table 1. PICO questions that served as the basis for recommendations and key concepts

Diagnosis
Question: Should cross-sectional imaging (CT or MRI) or EUS be used to diagnose CP in all patients suspected of having CP?
Question: Should s-MRCP vs non–secretin-enhanced MRCP be used to make the diagnosis of CP?
Question: Should direct vs indirect pancreatic function tests be used to make the diagnosis of CP?
Question: Should pancreatic histology vs imaging be used to make the diagnosis of CP?
Etiology
Question: Should multiple factor testing (toxic, idiopathic, genetic, autoimmune, recurrent acute, and/or obstructive) vs single-factor testing be used to make the diagnosis of CP?
Question: Should genetic testing vs no genetic testing be used to make the diagnosis of CP?
Natural history and clinical symptoms
Question: Does a defined etiology vs idiopathic disease determine important clinical outcomes in CP?
Question: Does BMI vs other etiologic factors determine the risk of developing endocrine insufficiency in CP?
Question: Does alcohol cessation vs no alcohol cessation alter the natural history of CP?
Question: Does tobacco cessation vs no tobacco cessation alter the natural history of CP?
Question: Should screening examinations vs no screening examinations for pancreatic malignancy be performed in patients with CP?
Management of pain
Question: Should interventional endoscopic or surgical therapy vs no interventional therapy be used in patients with CP who are actively consuming alcohol to improve pain symptoms?
Question: Should pancreatic duct decompression through endoscopy vs surgery be used in CP patients with evidence of pancreatic duct obstruction to improve pain symptoms?
Question: Should antioxidants vs no antioxidants be used in patients with CP to improve pain symptoms?
Question: Should opiates vs no opiates be used in patients with CP to improve pain symptoms?
Question: Should pancreatic enzymes vs no pancreatic enzymes be used in patients with CP to improve pain symptoms?
Question: Should celiac plexus blockade vs no celiac plexus blockade be used in patients with CP to improve pain symptoms?
Question: Should TPIAT vs no TPIAT be used to treat pain symptoms in patients with CP?
Question: Should experimental therapeutic modalities (i.e., radiation therapy, spinal cord stimulation, and transmagnetic brain stimulation) vs no experimental therapeutic modalities be used to treat pain symptoms in patients with CP?
Management of exocrine pancreatic insufficiency
Question: Should PERT vs no PERT be used in patients with CP to improve symptoms of pancreatic insufficiency?
Question: Should testing for vitamin deficiency vs no testing for vitamin deficiency be used in patients with CP and pancreatic insufficiency?

BMI, body mass index; CT, computed tomography; CP, chronic pancreatitis; EUS, endoscopic ultrasonography; MRCP, magnetic resonance cholangiopancreatography; PERT, pancreatic enzyme replacement therapy; s-MRCP, secretin-enhanced magnetic resonance cholangiopancreatography; TPIAT, total pancreatectomy with islet autotransplant.

a conditional recommendation are stated with "We suggest." The quality of evidence is graded from high to low. "High" quality evidence indicates that further research is unlikely to change the authors' confidence in the estimate of the effect, and that we are very confident that the true effect lies close to that of the estimate of the effect. "Moderate" quality evidence is associated with moderate confidence in the effect estimate, although further research would be likely to have an impact on the confidence of the estimate, whereas "Low" quality evidence indicates that further study would likely have an important impact on the confidence in the estimate of the effect and would likely change the estimate. "Very low" quality evidence indicates very little confidence in the effect estimate, and that the true effect is likely to be substantially different from the estimate of the effect.

Key concepts are statements that are not amenable to the GRADE process, either because of the structure of the statement or because of the available evidence. In some instances, key concepts are based on the extrapolation of evidence and/or expert opinion. The GRADE recommendations and key concept statements from this guideline are found in Tables 2 and 3, respectively.

DIAGNOSIS OF CP

Recommendation

1. We recommend computed tomography (CT) or MRI for the first-line diagnosis of CP. Either test should be the first choice for the diagnosis of CP. Endoscopic ultrasonography (EUS), because of its invasiveness and lack of specificity, should be used only if the diagnosis is in question after cross-sectional imaging is performed (strong recommendation, low quality of evidence).

Summary of evidence. The diagnosis of CP has been difficult because there is a debate about the gold-standard test that

Table 2. Recommendations on the management of CP

Diagnosis of CP
1. We recommend CT or MRI for the first-line diagnosis of CP. Either test should be the first choice for the diagnosis of CP. EUS, because of its invasiveness and lack of specificity, should be used only if the diagnosis is in question after cross-sectional imaging is performed (strong recommendation, low quality of evidence).
2. We suggest performing s-MRCP when the diagnosis of CP following cross-sectional imaging or EUS is not confirmed and the clinical suspicion remains high (conditional recommendation, low quality of evidence).
3. We suggest histological examination as the gold standard to diagnose CP in high-risk patients when the clinical and functional evidence of CP is strong, but imaging modalities are inconclusive (conditional recommendation, very low quality of evidence).
Etiology of CP
4. We recommend genetic testing in patients with clinical evidence of a pancreatitis-associated disorder or possible CP in which the etiology is unclear, especially in younger patients (strong recommendation, low quality of evidence).
Natural history and clinical symptoms of CP
5. We recommend alcohol cessation in patients with CP (strong recommendation, very low quality of evidence).
6. We recommend smoking cessation in patients with CP (strong recommendation, very low quality of evidence).
Management of pain in CP
7. We recommend surgical intervention over endoscopic therapy in patients with obstructive CP for the long-term relief of pain if first-line endoscopic approaches to pancreatic drainage have been exhausted or unsuccessful (strong recommendation, moderate quality of evidence).
8. We suggest considering the use of antioxidant therapy for CP with pain, although the benefit of pain reduction is likely limited (conditional recommendation, moderate quality of evidence).
9. We do not suggest the use of pancreatic enzyme supplements to improve pain in CP (conditional recommendation, low quality of evidence).
10. We suggest considering celiac plexus block for treatment of pain in CP (conditional recommendation, very low quality of evidence).
Management of exocrine pancreatic insufficiency in CP
11. We suggest PERT in patients with CP and exocrine pancreatic insufficiency to improve the complications of malnutrition (conditional recommendation, low quality of evidence).

CT, computed tomography; CP, chronic pancreatitis; EUS, endoscopic ultrasonography; PERT, pancreatic enzyme replacement therapy; s-MRCP, secretin-enhanced magnetic resonance cholangiopancreatography.

establishes the diagnosis. Furthermore, it represents a later stage of progressive disorders resulting in *irreversible morphologic damage* with variable clinical consequences. The diagnosis is made often using a combination of modalities, including exposure risk, underlying predisposition, cross-sectional imaging, and direct and/or indirect pancreatic function tests. In fact, likely the most useful diagnostic test for CP is a careful history and physical examination, as the pretest probability and clinical suspicion are integral for diagnosis—i.e., if the patient is in a high-risk group, the morphologic changes are a more accurate biomarker of CP rather than another disorder with a similar differential diagnosis. It is critical to assess the patient's risk factors for CP, including family and exposure history, the nature and character of the patient's pain, whether or not they have had previous episodes of acute pancreatitis, and whether they have related conditions such as steatorrhea and/or symptoms of vitamin deficiency.

However, in patients with clinical symptoms of an inflammatory disorder of the pancreas (e.g., previous episode of acute pancreatitis, characteristic pain, and/or maldigestion) and/or a suggestive gene–environment risk assessment, then cross-sectional imaging should be the first test used to establish the diagnosis of CP because it is universally available, reproducible, and valid when compared with other modalities.

No randomized controlled trials (RCTs) have been performed specifically comparing cross-sectional imaging with EUS for the diagnosis of CP with the caveat that the test characteristics of diagnostic modalities are generally not amenable to RCTs. The best evidence comparing modalities is from a systematic review and meta-analysis of 43 studies and 3460 patients with suspected CP in which the sensitivity estimates of EUS, MRI, and CT were 81% (95% confidence interval [CI]: 70%–89%), 78% (95% CI: 69%–85%), and 75% (95% CI: 66%–83%), respectively, and did not differ significantly from each other (19). Estimates of specificity were comparable for EUS (90%; 95% CI: 82%–95%), ERCP (94%; 95% CI: 87%–98%), CT (91%; 95% CI: 81%–96%), MRI (96%; 95% CI: 90%–98%), and ultrasound (US) (98%; 95% CI: 89%–100%). A limitation of this meta-analysis, however, was that not all the studies included a histologic gold standard to establish the type of inflammation for comparison.

Given the vast discrepancy in cost, availability, invasiveness, and objectivity, we believe that cross-sectional imaging should be the first-line test for the diagnosis of CP. Owing to its invasiveness and issues surrounding availability, intrarate reproducibility, and discrepancy over the definition and importance of specific diagnostic criteria, EUS should be used to diagnose CP alone if there is uncertainty following cross-sectional imaging (20).

Multiple other imaging modalities and scoring systems have been used to establish the diagnosis of CP, including contrast-enhanced EUS, ERCP, transcutaneous ultrasonography, and pancreatic elastography (6,21–24). However, high-quality RCT evidence is not available to warrant their inclusion as first-line diagnostic tests for CP in place of cross-sectional imaging or EUS.

Practical clinical approach. Demonstrating typical morphologic changes in the pancreas is a critical component of the definition of

Table 3. Key concept statements on the management of CP

Diagnosis of CP
1. Pancreatic function testing is an important means of diagnosing exocrine pancreatic insufficiency; however, its role in establishing the diagnosis of CP is complementary.
Etiology of CP
2. In patients with clinical features of CP, a comprehensive review of all risk factors should be performed. This provides information on the underlying mechanisms, identifies both fixed and modifiable risk factors, identifies potential targets for therapies, and provides clinically relevant prognostic information.
Natural history and clinical symptoms of CP
3. Identification of the disorders(s) underlying pancreatic inflammation is important in predicting progression to CP.
4. The development of DM in CP is most likely related to duration of disease, although other etiologic factors such as BMI and smoking status may incur an increased risk.
5. There is a lack of evidence to suggest that performing screening examinations on patients with CP to detect pancreatic malignancy is beneficial.
Management of pain in CP
6. Performing elective interventional procedures on patients who are actively using alcohol should be considered cautiously. Patients requiring urgent or emergent procedures for complications of CP should be considered separately.
7. Opiates may be considered to treat painful CP only in patients in whom all other reasonable therapeutic options have been exhausted.
8. TPIAT should be reserved for highly selected patients with refractory chronic pain in which all other symptom control measures have failed.
9. Experimental treatment modalities should be limited to use in the context of a clinical research trial.
Management of exocrine pancreatic insufficiency in CP
10. Patients with CP should have periodic evaluation for malnutrition including tests for osteoporosis and fat-soluble vitamin deficiency.

BMI, body mass index; CP, chronic pancreatitis; DM, diabetes mellitus; TPIAT, total pancreatectomy with islet autotransplant.

CP, as imaging is a surrogate for histology. In the absence of a universally agreed-on gold standard for the diagnosis of CP and the challenges in obtaining high-quality and representative histology, cross-sectional imaging is a familiar test for most clinicians and should be used as the initial test for diagnosis. Endoscopic US should be used if the diagnosis is still in doubt after cross-sectional imaging or if there is a concern about "minimal change disease" (CP without evidence of fibrosis) that cannot be visualized on cross-sectional imaging. There is not enough quality evidence to recommend a specific type of EUS scoring system, nor the number or types of criteria that should be used to definitively diagnose CP using this modality. Therefore, CP remains a clinical diagnosis, integrating and balancing the strength of evidence of the clinical scenario, the presence of risk factors, and the exclusion of other diseases in the differential diagnosis.

Recommendation

2. We suggest performing secretin-enhanced magnetic resonance cholangiopancreatography (s-MRCP) when the diagnosis of CP following cross-sectional imaging or EUS is not confirmed and the clinical suspicion remains high (conditional recommendation, low quality of evidence).

Summary of evidence. When the diagnosis of CP cannot be made following standard cross-sectional imaging or EUS, s-MRCP is suggested. s-MRCP allows for better visualization of the main- and side-branch ducts by stimulating the release of bicarbonate from the pancreatic duct cells. It also allows for quantification of the degree of filling into the duodenum, which may correlate with the severity of CP and help quantify the degree of pancreatic exocrine function (25–27). Given its expense, s-MRCP should be used only when the diagnosis is not confirmed with first-line testing.

There are no RCTs specifically evaluating the role of s-MRCP in the diagnosis of CP, although one systematic review has been performed (28). Evaluating 69 original articles and 15 reviews, the authors found that dynamic thick-slab 2-dimensional MRCP was the most used imaging sequence (86%). The diameter of the main pancreatic duct (75%) and pancreatic exocrine function based on visual grading of duodenal filling (67%) were the most evaluated pancreatic features. Smaller studies suggest the diagnostic value of secretin-enhanced studies in children with idiopathic CP and also in the identification of minimal change disease (29,30).

Practical clinical approach. If cross-sectional imaging and EUS are not diagnostic of CP, s-MRCP can be used to identify subtle ductal abnormalities such as dilated branches or an ectatic duct, which may indicate morphologic changes consistent with imaging criteria for CP. Structural imaging is a biomarker of the pancreas morphology and is most sensitive to changes caused by fibrosis with distortion of the ducts and calcifications. However, the diagnosis of CP should not be made solely on s-MRCP findings or other imaging modalities, as noted previously.

Key concept

1. Pancreatic function testing is an important means of diagnosing EPI; however, its role in establishing the diagnosis of CP is complementary.

Summary of evidence. There is controversy surrounding the use of pancreatic function tests to make the diagnosis of CP. Pancreatic function tests are used to make the diagnosis of EPI, and as most patients with CP do not have clinically significant EPI, the

sensitivity of pancreatic function testing to make the diagnosis of CP is low. This is due in part to the large reserve within the pancreas in which only significant loss of function (usually >90%) results in the clinically apparent symptoms of steatorrhea, azotorrhea, and resultant vitamin deficiency (31). However, there are patients whose only clinical manifestation of pancreatic exocrine cell damage may be EPI, and certainly, patients can have progressive EPI over their disease course. In fact, EPI represents an imbalance in at least 4 domains; nutritional intake, pancreatic digestive enzyme delivery to the small intestine, intestinal adaptation to disease, and nutritional needs of each type of essential nutrient. Thus, failure of the pancreas to deliver sufficient enzymes to meet a patient's nutritional needs is relative to the other 3 domains.

There are no RCTs, systematic reviews, or meta-analyses, which specifically detail the use of pancreatic function tests to diagnose CP. Based on the available evidence, the use of pancreatic function testing to diagnose CP therefore should only be used as an ancillary test in making the diagnosis (22,32–34).

There are multiple types of pancreatic function tests available and have historically been divided into direct and indirect types. The type of test used depends on clinical availability, provider expertise, patient tolerance, and expense. Table 4 details the type of pancreatic function testing available and the test characteristics of each.

Estimating the prevalence of exocrine insufficiency is difficult, as studies use a variety of methods and standards for diagnosis. Although a 72-hour fecal fat measurement might be considered the gold standard for complete failure, most studies use either clinical steatorrhea or reduced levels of fecal elastase as the primary diagnostic test. Neither of these is highly accurate, and the rate of clinically important maldigestion would likely be underestimated by these approaches. Fecal elastase is most commonly used, but a number of caveats apply to the use of this test. The accuracy of fecal elastase to detect EPI depends on the cutoff chosen. Some studies have used levels of <200 μg/g stool, but this level has a high false-positive rate. Lowering the cutoff to <100 μg/g stool improves specificity but lowers sensitivity (35). Although used historically, serum trypsin and/or trypsinogen tests are typically not currently performed because of reports of elevation in nonpancreatic pain syndromes and poor correlation with imaging findings.

Practical clinical approach. Having EPI does not independently establish the diagnosis of CP because there are conditions, such as CFTR variants that diminish bicarbonate secretion from birth, that sometimes do not result in loss of pancreatic tissue and morphologic change to the pancreas. Testing for EPI therefore should be used as an adjunctive test for patients in whom the diagnosis of CP has not been previously established.

Recommendation

3. We suggest histological examination as the gold standard to diagnose CP in high-risk patients when the clinical and functional evidence of CP is strong, but imaging modalities are inconclusive (conditional recommendation, very low quality of evidence).

Summary of evidence. When the diagnosis of CP cannot be made with cross-sectional imaging or EUS based on morphologic criteria, histologic evaluation is often considered. With the recent widespread use of EUS-guided fine-needle biopsy techniques, the ability to acquire pancreatic tissue for histologic analysis is safer

Table 4. Test characteristics of direct and indirect pancreatic function tests (110,111)

Test	Advantages	Disadvantages
Hormonal tests of pancreatic function		
CCK stimulation test (acinar cell stimulation measuring trypsin and/or lipase)	Direct acinar cell function Detects subtle EPI	Cumbersome Not widely available Specialized laboratory testing required Patient discomfort with Dreiling tube placement 2–3 hr test
Secretin stimulation test (ductal cell stimulation measuring bicarbonate)	Direct ductal cell function Performed endoscopically Uses laboratory autoanalyzer 60 min test Measures ductal secretory ability	Not widely available Prone to measurement error Risk and cost of endoscopy
Nonhormonal tests of pancreatic function		
Fecal elastace-1	Universally available Easily obtainable Noninvasive	Moderate sensitivity Limited specificity in diarrhea Limited use in mild disease
^{13}C-mixed triglyceride test	Easily obtainable High sensitivity (90%)	Not universally available Long test duration—4–6 hr
Serum trypsinogen/trypsin	Universally available Easily obtainable Noninvasive Quantifiable for tracking function over time	Does not measure digestive tract enzymes Elevated with pancreatic pain

CCK, cholecystokinin; EPI, exocrine pancreatic insufficiency.

and technically easier (36,37). However, the sensitivity of histologic evaluation for CP when tissue is available, compared with morphologic evaluation, is often no better than chance (38,39). Histologic evaluation can be limited because of sampling error, complications inherent in obtaining the biopsy sample, the patchy nature of pancreatic inflammatory changes, and histologic interpretation that is prone to subjectivity.

There are no RCTs, systematic reviews, or meta-analyses, which treat histologic evaluation as the diagnostic gold standard for CP. Nonetheless, histologic confirmation can serve as the diagnostic gold standard, its value most important for ruling out CP when the diagnosis is under consideration. Histologic evaluation should only be considered in high-risk patients after clinical, functional, and imaging tests have not established the clinicopathologic diagnosis and a thoughtful informed consent process has been had with the patient.

Practical clinic approach. Under the current clinicopathologic approach to disease, histology is the gold standard test to diagnose CP, and it is often used to "rule out" CP in patients in whom the diagnosis is being considered. However, both imaging and histology are biomarkers of an underlying disorder that may or may not be true CP, and thus, the sensitivity of histology to make the diagnosis is low. As the mechanistic model of disease is investigated and formalized further, histology will likely be less important in making the diagnosis of CP.

ETIOLOGY OF CP

Key concept

2. In patients with clinical features of CP, a comprehensive review of all risk factors should be performed. This provides information on the underlying mechanisms, identifies both fixed and modifiable risk factors, identifies potential targets for therapies, and provides clinically relevant prognostic information.

Summary of evidence. There are no RCTs, systematic reviews, or meta-analyses specifically focusing on the order of testing for determining an etiology of CP (40). The TIGAR-O system has been used to help categorize an etiology to explain CP, has proven useful in multiple international studies, and was recently revised to include new insights from the past 20 years (5,41). The acronym stands for T (Toxic-Metabolic), I (Idiopathic), G (Genetic), A (Autoimmune), R (Recurrent acute or severe pancreatitis), and O (Obstructive) (Table 5). The pancreatitis with Multiple risk factors-Alcohol consumption, Nicotine consumption, Nutritional factors, Hereditary factors, Efferent duct factors, Immunological factors, Miscellaneous and rare metabolic factors (M-ANNHEIM) system is a similar multirisk factor classification system that attempts to add information on disease activity and stage and has been used to evaluate the impact and interaction of various risk factors on the course of CP (22). The M-ANNHEIM system provides diagnostic criteria for etiology, clinical and diagnostic stage, and severity based on traditional clinicopathologic criteria (Table 6).

Practical clinical approach. The initial approach to evaluation of patients with suspected pancreatitis-related disorders and CP is to complete a thorough history and physical examination, along with biomarker tests. The history should include previous dates and number of episodes of acute pancreatitis (outlined in TIGAR-O or M-ANNHEIM), dates of onset of DM (if present), maldigestion/malnutrition, weight loss, bone health (e.g., fractures), renal disease, and diseases in organs associated with cystic fibrosis (e.g., lung disease, sinusitis, or male infertility). A family history should extend to at least third-degree relatives and include pancreatitis, cystic fibrosis, DM, and pancreatic cancer. The TIGAR-O checklist provides guidance for recording alcohol use, smoking, medications, toxins, DM, diet and key biomarkers including serum calcium, and triglycerides. Serum levels of fat-soluble vitamins and nutrition analysis also provide information on the possible disease stage. Imaging is also useful in identifying potential obstructive etiologies of pancreatic disease, including anatomical malformations, pancreatic stones, tumors, and other features. If the etiology is unclear, if the patient has a family history of pancreatic diseases, if the disease persists after therapeutic intervention (e.g., RAP after clearing the biliary system), or if the patient is young (e.g., less than 35 years of age), then genetic testing is indicated. It is also imperative to consider the differential diagnosis for CP, including autoimmune inflammation, inflammation and fibrosis arising from the pancreatic islet cells related to long-standing DM, renal disease causing secondary effects on the pancreas, medications that alter the immune system (e.g., cyclosporine), age-related atrophy or fibrosis, intraductal papillary mucinous neoplasms, acinar cell cystadenoma, the desmoplastic response to pancreatic neoplasm, inflammation upstream of a duct-obstructing mass, and other disorders (9).

Recommendation

4. We recommend genetic testing in patients with clinical evidence of a pancreatitis-associated disorder or possible CP in which the etiology is unclear, especially in younger patients (strong recommendation, low quality of evidence).

Summary of evidence. The past 2 decades have identified several genes associated with the diagnosis of CP. However, there are no RCTs, systematic reviews, or meta-analyses specifically evaluating whether patients with idiopathic CP should be offered genetic testing.

The primary goal of genetic testing is to identify underlying pancreatitis-related disorders that are contributing to the pathogenic process, to assist in decision making, and to help prevent the development of irreversible CP (2). Several pancreatitis-associated disorders can be identified that lead to significant changes in treatment strategy. The most well-known examples are *CFTR* variants with a CFTR-related disorder or cystic fibrosis, which can present as RAP or CP. Multiple other genes have been associated with the development of CP and its associated conditions (Table 7).

Genetic testing results provide important early information about the etiology of pancreatitis-related disorders. If the etiology of the pancreatitis-related disorder (such as characteristic pain and/or maldigestion) remains obscure, genetic testing can determine the genes, cell types, and mechanisms that are dysfunctional in the patient. This information drives confirmatory testing (e.g., sweat chloride for CFTR variants) for making a disease diagnosis and places the patient in a population of very high or very low disease prevalence, which affects the positive and negative predictive value of various biomarkers (2). Determining the etiology of a pancreatitis-related disorder may not lead to immediate treatment in some cases, but it does end often exhaustive, invasive, and expensive diagnostic testing for an advanced disease. Determination of the genetic etiology also informs decisions about more radical therapy for persistent or severe disease, such as total pancreatectomy with islet autotransplantation.

Table 5. The TIGAR-O Version 2.0 Pancreatitis System Risk/Etiology Checklist (short form) (41)

Toxic-metabolic
Alcohol-related (susceptibility and/or progression)
3–4 drinks/d
5 or more drinks/d
Smoking (if yes, record pack-years)
Nonsmoker (<100 cigarettes in lifetime)
Past smoker
Current smoker
Other, NOS
Hypercalcemia—(ionized calcium levels >12.0 mg/dL or 3 mmol/L)
Hypertriglyceridemia
Hypertriglyceridemic risk—(fasting >300 mg/dL; nonfasting >500 mg/dL)
Hypertriglyceridemic acute pancreatitis, history of (>500 mg/dL in the first 72 hr)
Medications (name)
Toxins, other
CKD—(CKD stage 5—ESRD)
Other, NOS
Metabolic, other
Diabetes mellitus (with the date of diagnosis if available)
Other, NOS
Idiopathic
Early onset (<35 yr of age)
Late onset (>35 yr of age)
Genetic
Suspected; no or limited genotyping available
Autosomal dominant (Mendelian inheritance—single-gene syndrome)
PRSS1 mutations (hereditary pancreatitis)
Autosomal recessive (Mendelian inheritance—single-gene syndrome)
CFTR, 2 severe variants in trans (cystic fibrosis)
CFTR, <2 severe variants in trans (CFTR-RD)
SPINK1, 2 pathogenic variants in trans (SPINK1-associated familial pancreatitis)
Complex genetics—(non-Mendelian, complex genotypes +/− environment)
Modifier genes (list pathogenic genetic variants)
PRSS1-PRSS1 locus
CLDN2 locus
Others
Hypertriglyceridemia (list pathogenic genetic variants)
Other, NOS
AIP/steroid-responsive pancreatitis
AIP type 1—IgG4-related disease
AIP type 2
RAP and SAP
Acute pancreatitis (single episode, including date of event if available)
AP etiology—extrapancreatic (excluding alcoholic, HTG, hypercalcemia, and genetic)
Biliary pancreatitis
Post-ERCP
Traumatic
Undetermined or NOS
RAP (number of episodes, frequency, and dates of events if available)
Obstructive
Pancreas divisum
Ampullary stenosis
Main duct pancreatic stones
Widespread pancreatic calcifications
Main pancreatic duct strictures
Localized mass causing duct obstruction

AP, acute pancreatitis; AIP, autoimmune pancreatitis; CKD, chronic kidney disease; ERCP, endoscopic retrograde cholangiopancreatography; ESRD, end-stage renal disease; HTG, hypertriglyceridemia; NOS, not otherwise specified; RAP, recurrent acute pancreatitis; SAP, severe acute pancreatitis.

Identification of genetic etiologies for pancreatitis-related disorders is also of value to the patient, although a "cure" may not be available. It can bring meaningful resolution to the etiology of poorly defined symptoms, connect them to disease-specific support networks, inform prognosis and comorbidities, and facilitate family planning. Genetic testing is of limited value in patients with end-stage CP because the underlying inflammatory processes have already irreversibly destroyed the pancreas. The exceptions are to identify genes associated with familial disorders and therefore to help family members make clinical decisions, to provide insight to the patient as to the etiology of CP beyond alcohol use and smoking, or to participate in a research study.

Genetic evaluation helps determine which pancreatic proteins have impaired function and which ones appear normal. This provides 2 types of information. (i) It tells that the pretest probability of true CP with early signs and symptoms is high, and (ii) it identifies the pathologic pathway—of which there are many. Thus, genetic testing may provide the clinical and early diagnosis before irreversible disease and guide choices of therapy. Note also that this approach allows many variables to be considered simultaneously within disease modes, so combinations of risk factors can be considered. Therefore, in pancreatitis-associated disorders, genetics is of central importance because it helps define the disease mechanism, provides prognostic information, and identifies targets for therapy.

Figure 1 details the recommendations for diagnosis of CP based on the traditional clinicopathologic model of disease. Figure 2 introduces diagnostic concepts in the context of the new mechanistic definition of CP. As more evidence develops in support of the mechanistic definition of disease, the authors believe that future guidelines will be more reliant on this new paradigm.

Table 6. The M-ANNHEIM scoring system for the grading of chronic pancreatitis severity (22)

Clinical Features	Points
Patient report of pain	
No pain without therapy (patient reports requiring no pain medication)	0
RAP (patient reports freedom from pain between attacks of acute pancreatitis)	1
No pain with therapy (patient reports freedom from pain with pain medication or endoscopic intervention)	2
Intermittent pain (patient reports intermittent pain-free episodes, either with or without therapy; possibly additional attacks of acute pancreatitis)	3
Continuous pain (patient reports absence of pain-free episodes, either with or without therapy; possibly additional attacks of acute pancreatitis)	4
Pain control	
No medication	0
Use of nonopioid drugs or use of mild opioids (WHO step 1 or 2)	1
Use of potent opioids (WHO step 3) or endoscopic intervention	2
Surgical intervention	
Pancreatic surgical intervention for any reason	4
Exocrine insufficiency	
Absence of exocrine insufficiency	0
Presence of mild, moderate, or unproven exocrine insufficiency not requiring enzyme supplementation (including patient reports of intermittent diarrhea)	1
Presence of proven exocrine insufficiency (according to exocrine function tests) or presence of marked exocrine insufficiency defined as steatorrhea (>7 g fat/24 hr), normalized or markedly reduced by enzyme supplementation	2
Endocrine insufficiency	
Absence of DM	0
Presence of DM	4
Morphologic status on pancreatic imaging (according to the Cambridge classification)	
Normal	0
Equivocal	1
Mild	2
Moderate	3
Marked	4
Severe organ complications	
Absence of complications	0
Presence of possibly reversible complications	2
Presence of irreversible complications	4
Severity index severity level point range	
M-ANNHEIM A	Minor 0–5 points
M-ANNHEIM B	Increased 6–10 points
M-ANNHEIM C	Advanced 11–15 points
M-ANNHEIM D	Marked 16–20 points
M-ANNHEIM E	Exacerbated >20 points

M-ANNHEIM scoring system points are added together, and the sum is used to categorize a patient's disease according to the M-ANNHEIM system.
DM, diabetes mellitus; M-ANNHEIM, pancreatitis with Multiple risk factors-Alcohol consumption, Nicotine consumption, Nutritional factors, Hereditary factors, Efferent duct factors, Immunological factors, Miscellaneous and rare metabolic factors; RAP, recurrent acute pancreatitis; WHO, World Health Organization.

Practical clinical approach. Testing for germline mutations (as opposed to acquired somatic mutations in tumors for cancer therapy) is not diagnostic of CP, but rather (i) identifies a population of patients with a high prevalence of pancreatitis-related disorders and CP so that it improves the accuracy of less sensitive or specific biomarkers and (ii) identifies the dysfunctional mechanism underlying the pathogenic processes that cause biomarkers to be abnormal and lead to disease. This is important in patients of any age because therapies (such as CFTR-modulating drugs) can target mechanism, and knowing the mechanism allows the most appropriate drug and/or therapy to be selected. It also provides prognostic information for the management of complex syndromes without specific treatment (i.e., for total pancreatectomy with islet autotransplant [TPIAT] assessment) and can provide answers to patients about the origin of their symptoms. In most instances, patients should be referred to a genetic counselor for evaluation; however, in centers in which experienced nongeneticist clinicians are comfortable ordering and evaluating the results, genetic referral is not necessary. At minimum, patients with idiopathic CP should be evaluated for *PRSS1*, *SPINK1*, *CFTR*, and *CTRC* gene mutation analysis, although more extended panels with over a dozen susceptibility and modifier genes, hypertriglyceridemia genes, and pharmacogenetics are available.

NATURAL HISTORY AND CLINICAL SYMPTOMS OF CP

Key concept

3. Identification of the disorders(s) underlying pancreatic inflammation is important in predicting progression to CP.

Summary of evidence. The primary clinical outcomes of patients with CP are debilitating abdominal pain, fat-soluble vitamin deficiency leading to malnutrition and related conditions such as osteoporosis, the risk of pancreatic malignancy, and the

Table 7. Summary of genetic polymorphisms implicated in CP (112,113)

Pathogenic gene	Inheritance pattern	Molecular/functional consequence	Clinical manifestations
Acinar cell dysfunction			
PRSS1 (cationic trypsinogen gene)	Complex low penetrance	Misfolding, ER stress	Recurrent AP and CP
CPA1 (carboxypeptidase A1 gene)	Complex low penetrance	Misfolding, ER stress	High relative risk of nonalcoholic CP
CEL (carboxyl ester lipase)	Autosomal dominant complex	Misfolding, aggregations misfolding, ER stress	MODY-8 pancreatitis
SPINK1 (serine protein inhibitor Kazal type 1)	Autosomal recessive	Loss of protein function due to the blocked active site of trypsin	2% of population Homozygotes with more severe disease
CTRC (chymotrypsin C)	Autosomal dominant	Activated trypsin resistant to degradation	Associated with early-onset pancreatitis
Ductal cell dysfunction			
CFTR (cystic fibrosis transmembrane conductance regulator)	Autosomal recessive	Loss of protein function due to failure of ductal bicarbonate secretion	2000 gene variants Widely divergent clinical presentation
Disease-modifying genes			
CASR (calcium-sensing receptor gene)	Autosomal recessive	Loss of ability to regulate intracellular calcium	Gain of function affects acinar cells; loss of function affects ductal cells
CTRC (chymotrypsin C)	Complex	Low expression effect potentiated by smoking	Pancreatitis when present with a trypsin-activating variant
CLDN2 locus (Claudin-2 gene locus)	Unknown	High risk with alcoholism	Accelerates transition from RAP to CP

AP, acute pancreatitis; CP, chronic pancreatitis; ER, endoplasmic reticulum; RAP, recurrent acute pancreatitis.

development of endocrine insufficiency manifesting as DM. At this stage, the disease is irreversible and preventive or restorative therapy is not possible. There have been no RCTs, systematic reviews, or meta-analyses specifically evaluating the etiology of pancreatitis and the natural history of pain.

The risk and etiologies of CP are well described, and the process leading to CP evolves over years—providing opportunities to intervene. Multiple studies now confirm that about 60% of CP cases evolved from acute pancreatitis and RAP, whereas about 10% of acute pancreatitis and 30% of RAP progress to CP. Within these studies, etiology plays a major role, with progression from acute pancreatitis to CP occurring twice as fast with alcoholic etiologies compared with genetic or idiopathic and 5 times faster than biliary acute pancreatitis (42). Genetic modifiers strongly affect the risk of progression from RAP to CP (43).

It has been suggested that painful CP, especially in patients with alcohol-induced disease, will improve over time (44). However, this finding has not been reproduced in further observational cohorts, and it generally accepted that the pain from CP does not "resolve" or "burn out" with time (45).

Fat-soluble vitamin deficiency resulting from decreased oral intake due to abdominal pain and malabsorption due to limited pancreatic enzyme production occurs in a minority of patients with CP. However, there are no RCTs, systematic reviews, or meta-analyses specifically evaluating the etiology of CP and the development of fat-soluble vitamin deficiency. In several large natural history studies, the prevalence of exocrine insufficiency ranges from 40% to 75% (46,47). The risk is highest in those with CP due to alcohol and/or tobacco use and in those with fibrocalcific (tropical) pancreatitis.

The risk of developing adenocarcinoma in patients with CP is relatively higher than the risk in the general population, but likely much lower than previously reported (48). Recent data suggest that in patients with well-characterized genetic polymorphisms putting them at risk for CP, the lifetime risk of developing pancreatic adenocarcinoma is between 5% and 10% (49). However, data are limited to case series and retrospective cohort studies.

Practical clinical approach. In general, a particular etiology of CP has not been proven to determine important clinical outcomes, such as rapid progression, EPI, chronic severe pain, or risk of malignancy. However, in certain well-characterized disease states such as autoimmune pancreatitis in which pain is not a frequent complication, etiology may determine outcomes and symptoms, and thus, identification of the disorder causing pancreatic inflammation can be important in predicting progression of CP.

Key concept

4. The development of DM in CP is most likely related to duration of disease, although other etiologic factors such as body mass index and smoking status may incur an increased risk.

Summary of evidence. The risk of developing pancreatic endocrine failure—type 3c DM—has not been demonstrated to result from any specific etiology of disease in patients with CP (50). The duration of disease is likely the most important etiologic risk factor for endocrine failure, and tobacco use may also play a role in the development of DM (10,51). There are no RCTs, systematic reviews, or meta-analyses specifically evaluating the risk of developing endocrine dysfunction in patients with CP.

Practical clinical approach. Although patients who are obese are more likely to have type 2 DM, patients with advanced CP are more likely to have low body mass index and T3cDM from islet cell loss. New-onset DM with weight loss is potentially also an indicator of pancreatic ductal adenocarcinoma.

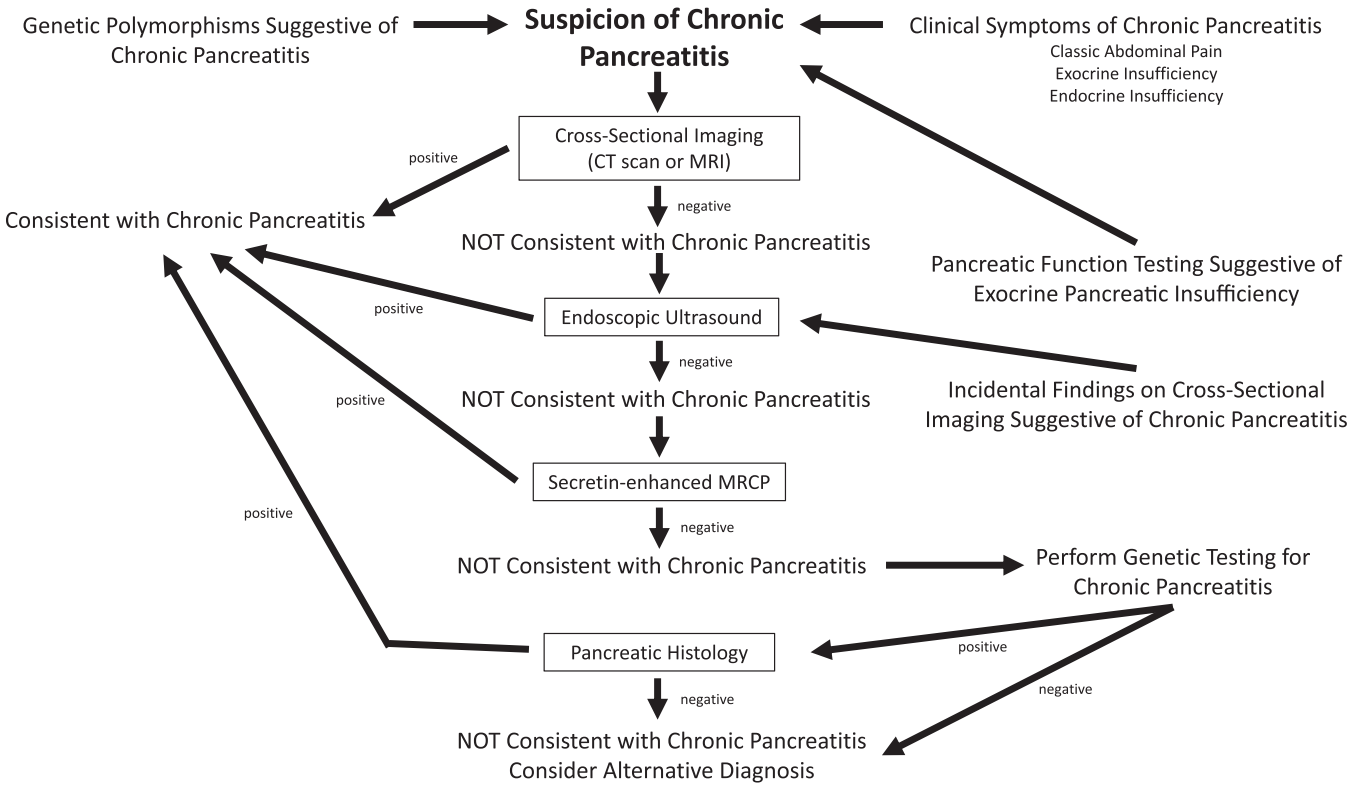

Figure 1. Diagnostic algorithm for chronic pancreatitis (CP) based on the clinicopathologic disease model of CP. This algorithm uses a symptom-first approach to diagnosis and does not stratify based on the etiology of disease or clinical risk factors. CT, computed tomography; MRCP, magnetic resonance cholangiopancreatography.

Recommendation

5. We recommend alcohol cessation in patients with CP (strong recommendation, very low quality of evidence).

Summary of evidence. There are no RCTs, systematic reviews, or meta-analyses, which address the issue of whether alcohol cessation alters the natural history of CP pain. However, several case series have suggested that discontinuing alcohol use improves the pain in CP but does not necessarily alter the progression to endocrine or exocrine dysfunction (52,53). There is 1 randomized trial, demonstrating that alcohol cessation counseling in patients admitted with an attack of acute alcoholic pancreatitis can limit further hospitalizations and pain attacks (54). Thus, alcohol cessation counseling is recommended for patients with CP, although the extent to which this intervention alters the natural history of the disease is unknown (55).

Practical clinical approach. Although the evidence is low quality, strict alcohol avoidance should be a cornerstone of any treatment program for patients with CP.

Recommendation

6. We recommend smoking cessation in patients with CP (strong recommendation, very low quality of evidence).

Summary of evidence. Smoking cessation is very challenging for patients, including those with CP (56). Smoking tobacco is widely believed to be a risk factor for the development of CP, but only single-center studies are available (57–59). There are no RCTs, systematic reviews, or meta-analyses specifically evaluating whether smoking cessation is beneficial in improving the natural history of CP. However, case series have reported a decrease in the amount of pancreatic calcification progression when smoking cessation occurs at the time of diagnosis of CP (60).

Practical clinical approach. Although the evidence is low quality, strict smoking avoidance should be a cornerstone of any treatment program for patients with CP, recognizing however that the long-term success rate of smoking cessation is low.

Key concept

5. There is a lack of evidence to suggest that performing screening examinations on patients with CP to detect pancreatic malignancy is beneficial.

Summary of evidence. There is very little quality evidence suggesting performing screening examination for pancreatic malignancy in all patients and even in those at high risk for pancreatic malignancy due to genetic or environmental risk factors. Although the overall prevalence of pancreatic malignancy is increased in patients with CP, there are no RCTs, systematic reviews, or meta-analyses to support screening this patient population for pancreatic malignancy (48).

Practical clinical approach. At this time, there is no definitive benefit to screen patients with CP for pancreatic ductal adenocarcinoma. This is based on the invasive and costly nature of testing, the inherent difficulty in screening given the structural changes of CP, and the inability to alter in many cases the natural

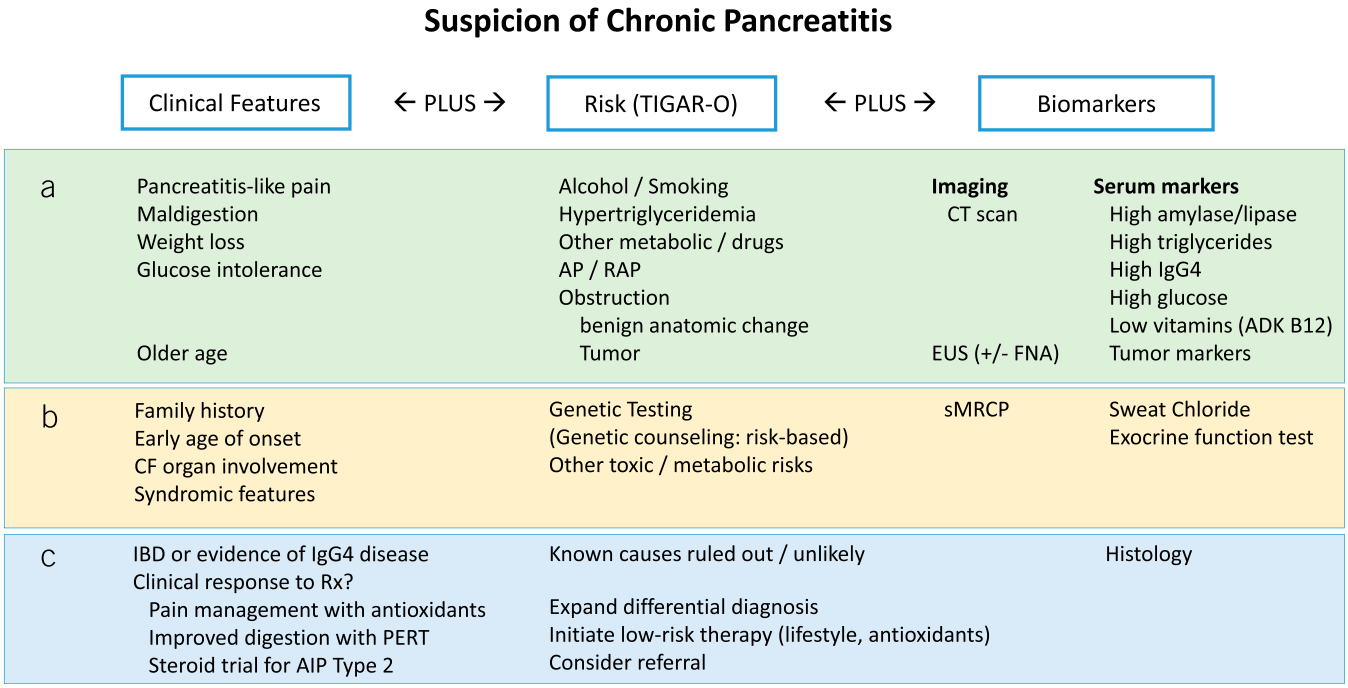

Figure 2. Conceptual diagnostic algorithm based on the new mechanistic definition of disease. With clinical suspicion of disease, this algorithm suggests the concordance of 3 features (clinical, risk, and biomarkers) to make a diagnosis, and it divides the approach into 3 levels of investigation (A, B, and C). Once a diagnosis is made, then the progressive workup can focus on issues related to management. AP, acute pancreatitis; AIP, autoimmune pancreatitis; CF, cystic fibrosis; CT, computed tomography; EUS, endoscopic ultrasonography; FNA, fine needle aspiration; IBD, inflammatory bowel disease; PERT, pancreatic enzyme replacement therapy; RAP, recurrent acute pancreatitis; Rx, therapy; s-MRCP, secretin-enhanced magnetic resonance cholangiopancreatography.

history of the disease even if malignancy is detected at an early stage.

MANAGEMENT OF PAIN IN CP

Key concept

6. Performing elective interventional procedures on patients who are actively using alcohol should be considered cautiously. Patients requiring urgent or emergent procedures for complications of CP should be considered separately.

Summary of evidence. The question of whether or not to undertake active interventions in patients with CP is complex and can be evaluated from both medical and social points of view. There are no RCTs, systematic reviews, or meta-analyses, which specifically address this issue.

From a medical point of view, it can be argued that it is ill-advised to undertake aggressive endoscopic or surgical interventions that may require ongoing or sequential procedures in a patient who is actively taking steps to harm themselves and exacerbate their underlying CP with ongoing and sustained alcohol abuse. Alcohol abuse may be causing or worsening the very pain that these endoscopic and surgical procedures are meant to treat, and if alcohol cessation could be obtained, some (or all) of these interventions may not even be warranted.

From a social point of view, patients with CP who continue to consume alcohol after appropriate patient education still warrant care and should be encouraged to stop alcohol use by means of counseling, attendance at Alcoholics Anonymous, and/or other programs. Urgent interventions should be performed in patients who continue to consume alcohol.

Practical clinical approach. In general, elective interventional procedures (such as celiac plexus interventions for pain palliation) should be performed with caution in patients who are actively consuming alcohol. Urgent interventions should be performed in patients who continue to consume alcohol given their medical necessity. Patients making good faith efforts to stop or reduce alcohol consumption but who still occasionally consume alcohol can be evaluated for interventional procedures on a case-by-case basis, recognizing the difficulties involved in alcohol cessation and the need to treat clinical symptoms of CP.

Recommendation

7. We recommend surgical intervention over endoscopic therapy in patients with obstructive CP for the long-term relief of pain if first-line endoscopic approaches to pancreatic drainage have been exhausted or unsuccessful (strong recommendation, moderate quality of evidence).

Summary of evidence. Patients with CP often experience pain in the setting of pancreatic duct obstruction. Duct obstruction can occur because of pancreatic duct stones, pancreatic duct strictures, or a combination thereof. Endoscopic decompressive procedures include ERCP with pancreatic sphincterotomy, stone clearance, stricture dilation, and pancreatic duct stenting. Other endoscopic options include interventional EUS procedures that usually involve placement of a transluminal stent to allow for pancreatic duct decompression. Several surgical decompressive procedures exist (Puestow, Frey, and Beger procedures) that may also include a component of partial

pancreatectomy. Unfortunately, there are no RCT or systematic review data, which reliably report whether successful or unsuccessful endoscopic decompression predicts subsequent successful drainage surgery.

Although widely performed, high-quality evidence regarding these procedures is limited. Cahen et al. (61) randomized 39 patients with CP to undergo either endoscopic or surgical drainage of the pancreatic duct. In this study, patients who underwent surgery had lower pain scores ($P < 0.001$) and better physical health summary scores ($P = 0.003$) when validated questionnaires were used. At the end of 24 months of follow-up, complete or partial pain relief was achieved in 32% of patients who underwent endoscopic drainage vs 75% of patients assigned to surgical drainage ($P = 0.007$). Complication rates, length of stay, and changes in pancreatic function were similar between the treatment groups. As would be expected, patients receiving endoscopic treatment required more interventions than patients who underwent surgery (a median of 8 vs 3, $P < 0.001$).

This same group published a long-term follow-up study of these 39 patients lasting 79 months (62). Among patients in the original endoscopic group, 68% underwent additional drainage compared with 5% who underwent surgery ($P = 0.001$). Length of stay and costs were equivalent in the 2 groups. Forty-seven percent of patients treated through endoscopy ultimately underwent surgery. Mean difference in validated pain scores was no longer significant (39 vs 22; $P = 0.12$), although surgery was superior in terms of pain relief (80% vs 38%; $P = 0.042$). Overall, patients' quality of life and pancreatic function were not felt to be different.

An older study also compared endoscopic with surgical therapy in patients with CP (63). This study included 140 patients, with a subgroup of 72 patients randomized to undergo either surgical resective or drainage procedures vs endoscopic therapy that focused on pancreatic sphincterotomy and stone removal. Patients in both groups had similar initial success rates, but the complete absence of pain was low in both groups and was more common in patients undergoing surgery (37% vs 14%), with the rate of partial relief being equivalent (49% vs 51%). Patients who underwent surgery gained more weight, whereas patients in both groups developed new-onset diabetes to an equal extent.

Various studies have compared outcomes between different types of pancreatic drainage procedures in patients with CP, with no surgery being clearly identified as superior (64–66). Factors such as local expertise likely play a major role in the selection of surgical procedure. It should be stressed that many of these studies are older, and since their publication, interventional endoscopic approaches are much more widely performed in the current era. Newer studies comparing endoscopic and surgical approaches are warranted.

Practical clinical approach. Although surgical approaches to pancreatic duct decompression have been shown to provide better long-term pain relief than endoscopic approaches, they are rarely first-line therapies and many surgeons only operate once endoscopic approaches to pancreatic drainage have been exhausted or unsuccessful. It is reasonable to perform endoscopic drainage procedures through ERCP and/or EUS in patients with a symptomatic, obstructed pancreatic duct as first-line therapy with surgery reserved for treatment failures or those unwilling to undergo multiple endoscopic treatments if ductal decompression is judged to be potentially successful. Means of ductal decompression, including the use of lithotripsy, should be at the discretion of the endoscopist based on local expertise.

Recommendation

8. We suggest considering the use of antioxidant therapy for CP with pain, although the benefit of pain reduction is likely limited (conditional recommendation, moderate quality of evidence).

Summary of evidence. Several studies have evaluated the question of whether or not antioxidant therapy has a benefit in treating pain in CP. The exact mechanism by which these agents could reduce pain is not fully clear; most theories propose that these agents reduce oxidative stress and provide an anti-inflammatory effect. If these agents were helpful, they could potentially be used as an alternative to other medications including narcotics.

A randomized trial from 2009 evaluated patients receiving a mixture of 5 antioxidant agents (daily doses of 600 μg organic selenium, 0.54 g ascorbic acid, 9,000 IU β-carotene, 270 IU α-tocopherol, and 2 g methionine) vs placebo. Patients also received analgesics on demand and daily pancreatic enzyme supplementation. At the end of 6 months, patients receiving antioxidants had significantly fewer painful days per month compared with the placebo group. Analgesic use was significantly less in those receiving antioxidants, and more patients receiving antioxidants became pain free (67).

A double-blind, randomized, controlled trial of antioxidant therapy (38.5 mg selenium yeast, of which 50 μg was L-selenomethionine, 113.4 mg D-α-tocopherol acetate, 126.3 mg ascorbic acid, and 480 mg L-methionine, together with the following secondary ingredients: 285.6 mg microcrystalline cellulose, 14.0 mg croscarmellose sodium, 7.0 mg colloidal anhydrous silica, and 3.0 mg magnesium stearate. The coating included 4.2 mg β-carotene.) vs placebo in 70 patients with alcohol-induced CP was also performed. Patients were followed up for 6 months by a variety of validated questionnaires. At the end of 6 months, there was no statistically significant difference in pain scores between groups. Opiate use, hospital admissions, and outpatient visits were similar between groups. These authors concluded that antioxidants did not improve pain or quality of life in patients with CP whose disease was due to alcohol (68).

A multimodality treatment approach, which included antioxidants and interventional therapeutic modalities, did result in long-term pain relief in a consecutive series of patients with painful CP, although this was not a RCT (69).

Two meta-analyses that included 9 and 12 trials, respectively, both found that overall antioxidants did appear to reduce pain, but that the effect size was small (70,71).

Practical clinical approach. Although the data for antioxidant therapy in patients with CP are limited, their scientific plausibility in CP is somewhat questionable and their use not Food and Drug Administration (FDA)-regulated; these agents appear to be safe and may reduce pain and can be considered for clinical use, especially early in the course of disease. The type of antioxidants used has widely varied in clinical practice, but clinical trials generally include at least selenium, ascorbic acid, β-carotene, and methionine. Unfortunately, the optimal type of antioxidants and dosage is not clear from previous studies.

Key concept

7. Opiates may be considered to treat painful CP only in patients in whom all other reasonable therapeutic options have been exhausted.

Summary of evidence. The question of whether to treat pain in CP with opiates has been debated for decades. Arguments in favor of opioid treatment include their efficacy and low cost. Arguments against opioid use include the risk of addiction, abuse, and tolerance as well as concerns about providing patients who may already have a history of substance abuse (i.e., alcoholism) with a narcotic agent. Side effects of narcotics (i.e., constipation) are also a concern. Physicians may also have valid concerns about prescribing narcotics in this setting. Despite its importance, few quality studies have evaluated this question, and no RCTs, systematic reviews, or meta-analyses on this subject exists to guide clinicians.

One trial evaluated the use of transdermal fentanyl vs sustained-release morphine tablets in 18 patients with CP. The study was a randomized cross-over trial. All patients were given immediate-release morphine tablets as a rescue medication. The authors concluded that transdermal fentanyl was not ideal for patients with CP because the dosage had to be increased 50% above the manufacturer's recommendation, and patients on transdermal fentanyl required significantly more rescue morphine administration (72).

Practical clinical approach. Overall, if possible, opiates should be avoided to treat pain in patients with CP given the risks of addiction, abuse, and tolerance. If a patient is unable to be palliated with other modalities, then opiates are justified for refractory pain. Patients who have been previously prescribed opiates for CP should be encouraged to transition to other medications. Ideally, the prescribing clinician (gastroenterologist/primary care provider/pain management center/and/or palliative care specialist) should be knowledgeable about the natural history of the disease and monitors the patient's symptoms and response to treatment over time as well as adheres to universal precautions for safe prescribing (i.e., screening for opiate use disorder, patient–provider prescribing agreement, annual urine drug screen, annual check of automated prescription systems, counseling for potential addiction, and wrap-around services for chronic pain).

Recommendation

9. We do not suggest the use of pancreatic enzyme supplements to improve pain in CP (conditional recommendation, low quality of evidence).

Summary of evidence. Patients with CP often receive pancreatic enzyme supplementation, typically to treat symptomatic EPI. Although the beneficial effects of treating EPI with pancreatic enzyme supplementation are established, their role as a treatment for pain is less clear. Although it seems plausible that pain due to cramping, diarrhea, and other EPI symptoms could be treated by enzyme supplementation, it is unclear whether these agents treat primary pancreatic pain due to inflammation, ductal stones, etc. This question has been addressed by several studies.

An older study of 26 patients with CP compared enteric-coated enzymes with placebo. Patients were treated for 4 months and then crossed over to the other medication. Overall, no difference was found when placebo and enzymes were compared. The authors concluded that pancreatic enzymes were not beneficial to the treatment of pain in patients with CP (73).

Since that study, many other studies have been performed and several Cochrane database reviews and meta-analyses have been performed. A 2009 Cochrane database review evaluated 10 randomized trials that included 361 patients. Although the study evaluated other outcomes besides analgesia, the analysis showed an equivocal result with regard to using enzymes to treat pain and felt that the available studies were of less than ideal quality (74).

A different meta-analysis regarding the potential analgesic effect of enzymes in patients with CP included 5 randomized studies. This study failed to show a meaningful effect in pain relief in patients using pancreatic enzymes, although 1 study did show a benefit to non–enteric-coated enzymes (75).

Finally, a meta-analysis of 6 randomized, double-blind, placebo-controlled trials failed to show a significant benefit from pancreatic enzyme therapy on pain associated with CP (76).

Practical clinical approach. Overall, pancreatic enzyme therapy should not be used as a form of pain control in patients with CP given their expense and general lack of clinical efficacy. However, patients with EPI usually derive some benefits in terms of relief from discomfort secondary to abdominal cramping, etc., from pancreatic enzyme replacement therapy (PERT). Nonetheless, if patients feel that their pain is improved on pancreatic enzyme therapy, especially non–enteric-coated formulations that have biologic plausibility, it is reasonable to continue these agents given their low risk of use and the lack of other low-risk analgesic alternatives.

Recommendation

10. We suggest considering celiac plexus block for treatment of pain in CP (conditional recommendation, very low quality of evidence).

Summary of evidence. Celiac plexus blockade refers to the injection of pharmaceuticals into and/or around the region of the celiac ganglia. The most common celiac plexus ingredients are a combination of a local anesthetic and a steroid, i.e., bupivacaine and triamcinolone (77). Celiac plexus blockade can be performed through endoscopy, interventional radiology, or surgical approaches. Advantages of celiac plexus blockade include the fact that a single treatment can potentially provide pain reduction or relief for 3–6 months, may reduce or eliminate the need for oral analgesia, and can be performed quickly and repeated as needed. Disadvantages of celiac plexus blockade include the risks of the procedure itself (bleeding, allergic reaction, etc.) and the risks of, and need for, sedation.

Although some studies have found that one approach is superior to another with endoscopic approaches often being favored, in general celiac plexus blockade is felt to be similarly effective whether it is performed by an endoscopist, a radiologist, or a surgeon (78,79). The decision to choose one type of physician over another can be made based on experience and availability.

A meta-analysis on the efficacy of celiac plexus blockade in patients with painful CP favored EUS-guided injections over percutaneous injections but acknowledged that the data regarding percutaneous injections were limited. This same analysis found a wide range of reported pain relief among patients (25%–96%) with a median response rate of EUS-guided procedures and percutaneous procedures of 68% and 61%, respectively. Overall, the authors felt that celiac plexus blockade was effective at relieving pain in CP (80).

The rationale behind the guideline recommendation is that there have been numerous studies as cited but most compared celiac plexus blockade with EUS vs a percutaneous approach. In addition, the clinical success (pain relief) varied significantly in the studies. "Selected patients" is added to highlight that numerous studies have not shown significant benefit in patients with CP.

Practical clinical approach. Celiac plexus blockade represents a relatively low-risk, opioid-free method to reduce refractory pain in certain patients with CP. Some patients can have a meaningful reduction in their symptoms, although it is not clear which patients will derive the most benefit. Celiac plexus blockade can be repeated on an "as-needed" basis, generally separating procedures by 3 months or more if the patient has had clinical benefit from the initial celiac intervention.

Key concept

8. TPIAT should be reserved for highly selected patients with refractory chronic pain in which all other symptom control measures have failed.

Summary of evidence. TPIAT is increasingly being used as a means of treating pain in patients with refractory painful CP. Offered at only selected centers, TPIAT is a procedure whose outcomes or effectiveness have not been subjected to RCTs, systematic reviews, or meta-analyses. Data consist exclusively of case series and cohort studies (81). As such, statements of its efficacy are limited, and it is critical that comparative effectiveness studies on important clinical outcomes be conducted in the future.

It is recommended that patients considering TPIAT be evaluated at an expert center in which multidisciplinary evaluation is available. Patients undergoing TPIAT for treatment of painful CP need to be thoroughly vetted and appraised of the subsequent risks of type 3c DM and potential lifelong intestinal dysmotility disorders.

Practical clinical approach. TPIAT should only be considered in patients in whom all medical treatment options have been exhausted. Resection procedures to treat painful CP should include discussion of islet cell replacement therapy.

Key concept

9. Experimental treatment modalities should be limited to use in the context of a clinical research trial.

Summary of evidence. In hopes of treating refractory CP pain, various experimental treatment modalities such as spinal cord nerve stimulation, transmagnetic brain stimulation, or direct radiation therapy to the pancreatic bed have been performed. Data on the efficacy of these modalities are limited to small case series and retrospective cohort studies. Therefore, it is recommended that use of these modalities be limited to a clinical research trial.

Practical clinical approach. All patients in whom medical and surgical interventions have failed for debilitating CP should be considered for referral to an expert center in which experimental therapies are offered.

MANAGEMENT OF EPI IN CP

Recommendation

11. We suggest PERT in patients with CP and EPI to improve the complications of malnutrition (conditional recommendation, low level of evidence).

Summary of evidence. The benefits of using PERT could include reduction in symptoms, gain of weight, improvement in fat absorption, improvement in fat-soluble vitamin and trace element levels, reduction in consequences of maldigestion (e.g., risk of bone fracture due to osteoporosis), improvement in quality of life, or reduction in mortality. For most randomized trials of PERT, the outcome of choice is the coefficient of fat absorption (CFA), measured over 72 hours. This is the outcome that the FDA requires for approval of these products. The FDA guidance to industry suggested a decrease in stool fat of 30% or more was clinically meaningful in those with a CFA of less than 40%, CFA must increase by at least 10%, and that studies would include at least 200 patients studied over 6 months (or 100 over 1 year). The normal CFA is >93% (only 7% or less of dietary fat is lost in the stool). Some studies also use measures of nitrogen (protein) absorption.

Seventeen randomized trials have been conducted on the use of PERT in patients with CP, 12 using a cross-over design, and 5 using a parallel design (82–98). Studies used enteric-coated capsules, non–enteric-coated tablets, microtablets, and granules, as well as used some agents that are not currently available. The daily dosage (in lipase USP/day) varied substantially across these studies from <50,000 to >700,000. Some studies compared one PERT product or one dosage against another, whereas some compared PERT against placebo. The timing of PERT ingestion varied, with some using before meals and some during meals. Some studies added an H2 inhibitor of proton-pump inhibitor in addition to the PERT.

A Cochrane database review in 2009 assessed the efficacy of PERT therapy in reducing pain, improving steatorrhea, and improving quality of life (74). The analysis of 10 RCTs, comprising 361 patients, noted no identifiable improvement in pain or reduction in analgesic use. The use of enzymes did significantly reduce fecal fat and demonstrated a nonsignificant trend to improvement in weight and improvement in quality of life. This review concluded that the data were equivocal and urged additional studies. A more recent meta-analysis analyzed 17 trials (99). This analysis noted that 14 trials included data on the CFA comparing PERT vs baseline, PERT vs placebo, and PERT vs PERT. PERT improved the CFA compared with baseline significantly (83.7% ± 6.0 on PERT, vs 63.1 ± 15.0 baseline, $P < 0.00001$). Fecal nitrogen excretion and stool weight were also reduced ($P < 0.001$). In some studies, PERT also improved flatulence and fecal consistency. Seven studies compared PERT with placebo. PERT increased the CFA compared with placebo (83.2 ± 5.5 vs 67.4 ± 7.0, $P = 0.0001$, high heterogeneity $I^2 = 86\%$). Four studies analyzed high-dose vs low-dose PERT and noted a slightly higher CFA with dosages of lipase >60,000 units daily (not significant). This analysis concluded that PERT improved fat and protein absorption, compared with baseline or placebo.

All the original studies included in this meta-analysis had a maximum follow-up of only 2 months. A few long-term follow-up studies over longer periods have noted significant improvement in nutritional parameters, weight, symptoms, and quality of life (100–102). There are no data on the effect of PERT in preventing consequences of maldigestion (bone fracture). Retrospective studies (23) have suggested EPI may have a detrimental effect on mortality, but there are no data on whether PERT may improve this condition (103).

Practical clinical approach. EPI should be suspected in those with long-standing CP or in those with CP and weight loss, malnutrition, diarrhea, steatorrhea, osteoporosis, or osteopenia. In fact, a clinical suspicion is often sufficient to make the diagnosis without formal fecal fat measurement in the proper clinical

context, with titration of pancreatic enzymes to improve symptoms. An abnormal fecal elastase is the most easily available diagnostic test. Therapy should include an adequate dosage (at least 40,000–50,000 USP units of lipase with each meal) administered during the meal. The measurement of fat-soluble vitamin levels and bone density at baseline and periodically thereafter are appropriate.

Key concept

10. Patients with CP should have periodic evaluation for malnutrition, including tests for osteoporosis and fat-soluble vitamin deficiency.

Summary of evidence. Testing for consequences of malnutrition is frequently performed, although there are no RCTs, systematic reviews, or meta-analyses to provide evidence for this practice. Single-center studies have demonstrated an increased risk of osteoporosis and subsequent fracture risk in patients with CP (104–106). One RCT did evaluate the use of intramuscular vs oral vitamin D to achieve vitamin D sufficiency in CP and found the intramuscular route to be more efficacious (107). No studies have been performed to determine the most appropriate test for bone loss.

Patients with CP are at risk for fat-soluble vitamin deficiency, as well as zinc and magnesium deficiency, regardless of whether they have proven EPI (108,109). The degree of abnormality likely corresponds to the degree of EPI. There are no RCTs, systematic reviews, or meta-analyses, which have evaluated the role of testing for these deficiencies on important patient outcomes in CP. Nor there are RCTs, systematic reviews, or meta-analyses evaluating the role of dietary interventions specifically in CP.

Practical clinical approach. Although there is little high-quality evidence behind this practice, periodic evaluation of fat-soluble vitamin and zinc deficiency should be considered in patients with CP given their higher fracture risk and overall increased incidence of malnutrition. In the absence of high-quality evidence, it is generally recommend that small, frequent meals without fat restriction should be advised in patients with CP.

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CONFLICTS OF INTEREST

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