Clube Português do Pâncreas

CHRONIC PANCREATITIS

CPP Recommendations

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List of abbreviations

AEs	Adverse events
AIP	Autoimmune pancreatitis
CCK	Cholecystokinin
CEH-EUS	Contrast-enhanced harmonic endoscopic ultrasound
CFA	Coefficient of fat absorption
CO_2	Carbon dioxide
CP	Chronic pancreatitis
CT	Computed tomography
DM	Diabetes *mellitus*
DM3c	Type 3c diabetes *mellitus*
DPPHR	Duodenal preserving pancreatic head resection
E-EUS	Endoscopic ultrasound elastography
ePFT	Endoscopic secretin / pancreatic function test
ERCP	Endoscopic retrograde cholangiopancreatography
ESGE	European Society of Gastrointestinal Endoscopy
ESPEN	European Society for Clinical Nutrition and Metabolism
ESWL	Extracorporeal shock wave lithotripsy
EUS	Endoscopic ultrasound
EUS-FNA	Endoscopic ultrasound-guided fine needle aspiration
FCSEMS	Fully covered self-expanding metal stent
IAT	Islet cell auto-transplant
LAMS	Lumen-apposing metal stent
MPD	Main pancreatic duct
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
MRI+MRCP	Magnetic resonance imaging with cholangiopancreatography
PD	Pancreatic duct
PDD	Pancreatoduodenectomy
PEI	Pancreatic exocrine insufficiency
PERT	Pancreatic enzyme replacement therapy
PPI	Proton pump inhibitor
RCT	Randomized clinical trials
s-MRCP	Secretin-enhanced magnetic resonance cholangiopancreatography
TP	Total pancreatectomy
TP-IAT	Total pancreatectomy with islet cell auto-transplant
UEG	United European Gastroenterology
US	Transabdominal ultrasound

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INTRODUCTION

Pedro Moutinho Ribeiro

Chronic pancreatitis (CP) is used to describe a syndrome of chronic inflammation of the pancreas, most often seen in alcoholics and smokers, and, rarely, in genetically predisposed individuals, that results in progressive scarring of the pancreatic tissue with consequent loss of function. Recent studies point to an increasing incidence of CP over the past decade, which probably reflects an improvement in diagnosis and changes in disease definition.

In terms of pathophysiology, CP is fairly complex and remains incompletely understood. Acinar cell injury, stress responses, duct dysfunction, persistent or altered inflammation and/or neuro-immune crosstalk are mechanisms often implicated in the progressive and definitive destruction of the pancreatic parenchyma.

Functional consequences include recurrent or constant abdominal pain, diabetes *mellitus* (endocrine insufficiency) and maldigestion (exocrine insufficiency) with consequent malnutrition.

The diagnosis of CP remains challenging in early stages of the disease, as its initial presentation is usually ill-defined and overlapped with other digestive disorders.

On the other hand, in later stages patients often present with abdominal pain, steatorrhea and diabetes, as well as numerous acute and chronic complications. These late stages are characterized by variable degrees of fibrosis and may present with calcification of the pancreatic parenchyma, obstruction, dilatation and stricturing of the pancreatic ducts, pseudo-

cysts, vascular complications and even obstruction of the common bile duct and/or duodenal lumen.

Clinical diagnostic tools have also seen considerable improvement with advances in (echo)endoscopic and radiologic imaging techniques, along with the widespread use of pancreatic function tests in clinical routine.

The aims of medical treatment include lifestyle modifications, nutrition, exocrine and endocrine pancreatic insufficiencies correction and pain management. Although evidence-based consensus is still limited, the other therapeutic options comprise endoscopic and surgical interventions. The most common indications for endoscopic procedures are strictures of the pancreatic duct, obstruction of the common bile duct and pancreatic pseudocysts.

Surgery retains a major role in the management of CP patients with intractable chronic pain or suspected pancreatic mass. Other complications like biliary and gastroduodenal obstructions, pseudocysts and gastrointestinal hemorrhage can also be treated surgically, especially in cases where other therapeutic interventions fail.

With this manuscript entitled "Chronic Pancreatitis – CPP Recommendations", the Board of the *Clube Português do Pâncreas* pretends to provide an educational and updated document, helpful to physicians interested in pancreatic pathology, especially those involved in the management of CP patients.

We have focused particular attention on the pathophysiology and natural history of CP as well as the diagnostic workup and therapeutic management of principal symptoms and complications of this disease.

2

FROM PATHOPHYSIOLOGY TO NATURAL HISTORY

Richard Azevedo and Ana Caldeira

2.1. Epidemiology

Few population-based studies on the incidence, prevalence and natural history of CP have been performed [1]. Thus, its epidemiological characteristics are not well defined [2].

Reported annual incidence, roughly similar in all countries, ranges from 5 to 14 cases per 100 000 individuals [1, 3] with a prevalence of approximately 30-50 per 100 000 individuals, according to a recent population-based study [4].

Latest studies point to an increasing incidence of CP over the past decade, which probably reflects an improvement in diagnosis and changes in disease definition [1], as alcohol consumption and smoking levels have been relatively stable [5].

CP is up to 5 times more frequent in men than in women [6] and is more common in black individuals [2]. Its prevalence increases with age and the median age at diagnosis ranges between 51 and 58 years [6]. Younger ages of onset are mostly related to genetic factors [1].

2.2. Pathophysiology

The pathophysiology of CP is fairly complex and remains incompletely understood [3]. CP is characterized by ongoing inflammation of the pancreas, leading to progressive loss of the endocrine and exocrine compartment due to atrophy and replacement with fibrotic tissue [1]. This fibrosing process ultimately leads to a progressive loss of the lobular morphology and structure of the pancreas, deformation of the

large ducts and marked changes in the arrangement of the islets [7].

Pancreatic stellate cells play a major role in pancreatic injury [7] because, during pancreatitis, they are activated in response to oxidative stress, cytokines, growth factors and toxins. These activated pancreatic stellate cells secrete excessive amounts of extracellular matrix proteins which will lead to pancreatic parenchymal fibrosis [8].

Five mechanisms have been proposed to be involved in the pathophysiologic process of CP [1]:

// **The necrosis-fibrosis sequence hypothesis.** After repeated episodes of acute pancreatitis, the repair of damaged regions by pancreatic stellate cells gives rise to the replacement of necrotic pancreatic parenchyma with fibrotic tissue [9].

// **The sentinel acute pancreatitis event hypothesis.** A single episode of acute pancreatitis activates pancreatic stellate cells, leading to fibrosis due to ongoing injury and stress [9].

// **Acinar cell injury.** Direct metabolic-toxic effect of environmental factors (alcohol and tobacco) may cause injury in acinar cells [10].

// **Acinar stress responses.** Oxidative stress due to free radicals in acinar cells leads to multiple cytokines release [11].

// **Ductal dysfunction.** It leads to the formation of protein-rich plugs and upstream ductal obstruction which causes inflammation and pancreatic ductal-hypertension with subsequent hypoperfusion, ischemic injury of the acinar cells and pancreatic parenchymal fibrosis [2].

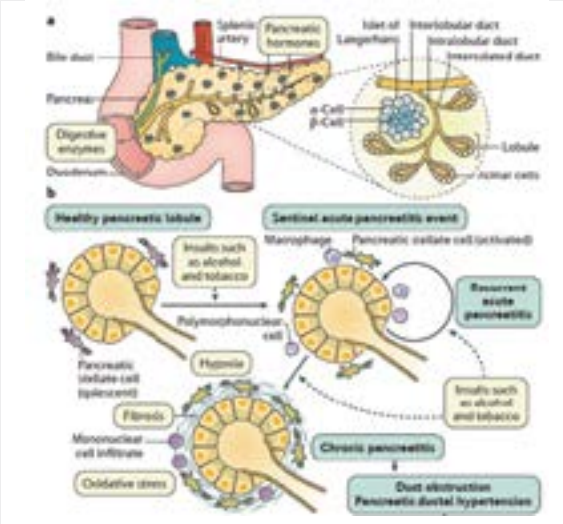

FIGURE 1
PATHOPHYSIOLOGY OF CHRONIC PANCREATITIS
a. Anatomy of a healthy pancreas
b. Pathophysiology of chronic pancreatitis after the first episode of acute pancreatitis
Adapted from Kleeff *et al.* [1]

2.3. Etiology and risk factors

The etiological risk factors associated with CP are multiple and involve both genetic and environmental factors [7]. The TIGAR-O classification of CP proposes risk modifiers that may interact with each other to produce pancreatic disease [11] - table 1.

The etiology of CP varies according to gender, being alcohol abuse and tobacco smoking the major causes in men and idiopathic and obstructive factors the most common causes in women [1].

Toxic-metabolic

ALCOHOL

The most prevalent cause of CP remains chronic alcohol abuse, with 40-70% of all cases of CP in western countries being attributed to alcohol [1]. The pathogenesis of alcoholic pancreatitis is poorly understood, but direct toxicity of alcohol metabolites to acinar cells seems to play an important role [1, 2].

Alcohol increases the risk of CP in a dose-dependent manner [2]. Although there is no true threshold below which the disease does not occur [3], in nearly all patients with CP at least 5-10 years of intake exceeding 60-80 grams of ethanol per day are required for CP development [1, 2].

Overall, less than 10% of heavy drinkers develop alcoholic-induced pancreatitis [7], suggesting that other cofactors play an important role [3]. Alcohol sensitizes the pancreas to other external factors, such as smoking, diet or genetic predisposition, which interact to increase alcohol toxicity [7] Cigarette smoking appears to be the strongest association, with some studies reporting that 90% of patients with alcohol-induced CP are also chronic smokers [12].

Many patients with alcoholic CP have an early phase of recurrent attacks of acute pancreatitis, which may last 5 to 6 years, followed by later development of chronic pain and endocrine/exocrine insufficiency [3].

TOBACCO

Tobacco smoking is an independent risk factor for CP and accelerates the disease course [7]. The association between smoking and CP is dose-dependent [2]

and the relative risk of developing CP is more than 3-fold higher in heavy smokers (>1 pack/day) [3].

Heavy smokers have a significantly increased risk of developing pancreatic calcifications [7] and smoking cessation after clinical onset of CP reduces the risk of subsequent calcifications [3].

Smoking significantly increases the rate of secondary pancreatic cancer and overall mortality in patients with CP [3].

Non-alcohol and non-tobacco-associated chronic pancreatitis

Non-alcohol and non-tobacco-associated CP accounts for 20-50% of cases in western countries [1].

GENETIC

Hereditary pancreatitis is a rare cause of CP (prevalence of approximately 0.3 per 1 000 0000 individuals) [1], and only one type of mutation appears sufficient to cause the disease: mutations in the PRSS1 gene (which encodes trypsin 1) [3] leading to premature trypsinogen activation [2]. The inheritance pattern is autosomal dominant with an incomplete penetrance (80%).

All other identified mutations and polymorphisms should be considered as cofactors, mutations that increase susceptibility or as modifier genes that increase the severity of disease [3]. Probably, combinations of polymorphisms and mutations work together to determine the susceptibility to disease.

Mutations in two genes encoding proteins involved in controlling intrapancreatic trypsin 1 activity are strongly associated with recurrent acute and CP: SPINK1 and CTRC. Also, mutations in the CFTR genes are commonly identified whereas mutations in other genes are less frequently identified.

AUTOIMMUNE

Autoimmune pancreatitis (AIP) represents 2-4% of cases of CP and encompasses two different chronic entities [13].

In type 1 AIP, patients are usually older than in type 2, with a mean age at disease onset of 60-70 years [3, 7]. Involvement of other organs occurs in about 60% of patients (biliary strictures, retroperitoneal fibrosis, pseudotumors and sialoadenitis). Many of the plasma cells and CD4+ T cells that infiltrate the pancreas express IgG4 on their surface and elevation in serum levels of IgG4 can be found in about 2/3 of patients [3].

Type 2 AIP, less frequent than type 1 and typically occurring in younger patients (40-50 years) [7], is limited to the pancreas and is not associated with an infiltration of IgG4+ cells [13].

IDIOPATHIC

Idiopathic CP represents 10-30% of cases of CP [7] and is more common in women [3]. Many cases labeled as idiopathic CP may be due to certain less severe CFTR and SPINK1 genes mutations. Therefore, many patients are probably mislabeled and interpreting idiopathic CP literature is difficult.

Idiopathic CP can present in two different forms: an early-onset type (appearing in the late second or third decade of life) and a late-onset form (in the sixth or seventh decade) [3].

Tropical pancreatitis, also known as fibrocalculous pancreatic diabetes, is a form of idiopathic early-onset pancreatitis mainly reported in developing countries [13]. Southern India has the highest prevalence of this form of CP [2].

OBSTRUCTIVE

Obstruction of the main pancreatic duct, which can be divided into benign and malignant causes, leads to chronic obstructive pancreatitis upstream of the obstruction [2].

Benign strictures may develop after a severe attack of acute pancreatitis, blunt or penetrating trauma, duodenal wall cysts or sphincter of Oddi stenosis or dysfunction [11]. Pancreas ***divisum***, a common normal variant, is not often considered a cause of CP [3]. Many patients with pancreas ***divisum*** often have coexistent genetic mutations that may explain CP [2]. However, few patients may present CP confined to the dorsal pancreas, suggesting a causative role of ductal obstruction in CP in these patients [2].

Acquired strictures of the main pancreatic duct can also occur as a consequence of tumor obstruction (adenocarcinoma, islet cell tumor, intraductal papillary mucinous neoplasms or ampullary neoplasms) [3].

RECURRENT AND SEVERE ACUTE PANCREATITIS

Recurrent episodes of acute pancreatitis may lead to the development of a chronic inflammatory response, culminating in CP. This can also occur even with just one severe attack of acute pancreatitis, usually associated with significant pancreatic necrosis and the need for surgical necrosectomy [3].

TOXIC-METABOLIC	Alcohol Tobacco Hypercalcemia Hypertriglyceridemia Chronic kidney disease Medications
IDIOPATHIC	Tropical chronic pancreatitis Early-onset Late-onset
GENETIC	Autosomal dominant: hereditary pancreatitis PRSS1 mutations Autosomal recessive/Modifier genes CFTR mutations SPINK1mutations CTRC mutations Others
AUTOIMMUNE	Type 1 (IgG4-related) and type 2
RECURRENT AND SEVERE ACUTE PANCREATITIS	Post-necrotic (after severe necrotizing pancreatitis) Vascular disease/ischemia
OBSTRUCTIVE	Pancreas *divisum* Sphincter of Oddi disorders Malignant pancreatic duct obstruction Post-traumatic pancreatic duct scars and strictures

TABLE 1
ETIOLOGIES OF CHRONIC PANCREATITIS ACCORDING TO THE TIGAR-O SYSTEM

2.4. Natural history and prognosis

Natural history can be divided into 3 phases, with huge overlap [14]:

// Early phase: encompasses the first 5 years of the disease and it is characterized by acute pancreatitis episodes, pain and hospitalizations.

// Middle phase: lasts 5-10 years and presents with less acute manifestations. Morphological changes (duct strictures and pancreatic calcifications) become evident.

// Late phase: from approximately 10 years onwards. Acute manifestations become rare and symptoms of endocrine and exocrine insufficiency emerge.

The progression and duration of each phase is highly variable and dependent on the etiologic factors of CP. Furthermore, the sequence of events can occur in all possible manners.

The prognosis of CP is variable and largely depends on the presence of ongoing alcohol consumption, in patients with alcoholic CP, and associated cigarette smoking. Sustained alcohol intake increases mortality risk by an additional 60% [3].

The incidence rate of pancreatic cancer in patients with sporadic pancreatitis and a minimum 5-years follow-up is around 14.4% [1]. The cumulative proportion of patients with pancreatic cancer in this population 20 years after CP diagnosis is 4% [1].

Concerning hereditary CP, the cumulative proportion of patients with pancreatic cancer is 1.5% at 20 years, 8.5% at 40 years and 25% at 60 years after symptoms onset [1].

The cause of death in patients with CP is usually related to other medical conditions associated with smoking, alcohol abuse, pancreatic cancer and post-operative complications rather than CP itself [3]. Ten-year and twenty-year survival in patients with CP is approximately 70% and 45%, respectively [3].

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3

DIAGNOSIS

3.1. Clinical diagnosis

Teresa Antunes

Diagnosing chronic pancreatitis (CP) can be challenging because it is a heterogeneous disease, with different causes and a long delay between onset and full classic presentation. Despite of all the progress in technology and major steps in quality of morphologic procedures, as seen in the latest years, this delay has not improved significantly.

Clinical presentation depends on the stage of the disease. In earlier stages recurrent episodes of acute pancreatitis are the major signs dominating clinical presentation.

As the inflammatory process goes on, less acute episodes occur and pain adopts different aspects or may even disappear. After 10 to 15 years from onset, functional insufficiency becomes present [1]. Then, classic presentation with pain, pancreatic exocrine and endocrine insufficiency appears.

Pain

Abdominal pain, most frequently epigastric, is the trigger symptom to start considering the diagnosis of CP. Pain may manifest in a multiplicity of forms. It can be present in short episodes, separated by long pain-free periods, or the opposite: chronic daily epigastric pain punctuated by severe exacerbations, that may require hospitalization, and short pain-free intervals.

Although pain is the dominant symptom, around 20% of the patients may be completely asymptomatic [2].

A majority of authors accept that, at late stages of the disease, the intensity of pain is significantly reduced correlating to long lasting inflammation and the appearance of fibrosis - the burnout theory [3]. Not all studies are in agreement, however, it is not possible to predict in an individual patient if pain will diminish, remain stable or intensify over time.

Alcohol is the most frequent cause of disease in western countries and alcohol intake is related to a faster onset of symptoms, earlier presence of calcifications and earlier diagnosis. Due to different tolerance "thresholds", even moderate amounts of alcohol can induce CP.

Although pathophysiology is not the subject of this topic, it is important to emphasize the role of a broad range of events such as mononuclear cell infiltration, inflammation, its mediators, fibrosis development, protein plugs, stone formation, calcifications and ductal changes. All these steps contribute to the onset and maintenance of pain. Besides, late stages are frequently associated with complications in and around the pancreas such as biliary obstruction and vascular thrombosis, which, by themselves, are also pain promoters.

Pancreatic exocrine insufficiency

Pancreatic juice consists of water and bicarbonate (both secreted by ductal cells), and enzymes: amylase, lipase, trypsin(ogen), chymotrypsin(ogen), (pro) elastase, (pro)carboxypeptidase, fosfolipase A2 and carboxylesterase secreted by acinar cells [1]. Normal pancreas secretes around 1500 mL/day of a clear isotonic alkaline fluid. Pancreatic secretion is mediated by both neuronal and hormonal mechanisms. In basal conditions (fasting) bicarbonate concentration is 80 mmol/L approximately.

Secretin and cholecystokinin are the major mediators, but other mediators are also known to play a role (such as gastrin-release peptide, vasoactive intestinal peptide and substance P).

Food intake is the natural stimulant of pancreatic secretion. After a regular meal there is an increase of water and bicarbonate flow and enzymes are also secreted in considerable amounts, adopting a plateau pattern. Pancreatic exocrine insufficiency (PEI) is clinically evident only when 90% of the function is lost, which is classically related to a large functional reserve of the pancreas [4]. However, more recent studies have demonstrated the important role of gastric lipase output, which is increased 3- to 4-fold in patients with PEI, that also has a relevant function on triglyceride digestion. This is a compensatory mechanism for pancreatic lipase deficiency and explains, at least in part, the absence of steatorrhea in mild and moderate stages of disease with more than 10% of pancreatic lipase secretion [5].

Clinically, steatorrhea is the most prominent symptom of PEI. The usually described loose and greasy voluminous stool appearance is present only in overt steatorrhea, while slight to moderate elevation of fecal fat content may be completely unnoticed. Lipid malabsorption is more evident and precedes, for a long period (years), the overt malabsorption of proteins and carbohydrates. In early stages, the intraluminal lipolytic activity is reduced (low levels of bicarbonate in pancreatic fluid reduce lipase stability during small bowel transit). Maldigestion of fat and its presence in distal ileum causes alteration of motility leading to abdominal pain and bloating, and stool appearance may still be normal or diarrhea (but not yet steatorrhea) may be present [6].

Malabsorption of fat soluble vitamins may occur, but clinical symptomatic vitamin deficiency is rare [7]. The absorption of calcium, magnesium and essential fatty acids is also impaired, and significant bone loss may be present [4].

Another late onset complication of PEI is the appearance of cardiovascular events [8]. Malabsorption of both, fatty acids and amino acids, leads to reduced plasma levels of high-density lipoprotein C and A, which are protectors against atherogenesis [9].

As a result of exocrine insufficiency, weight loss is expected anytime. Nutritional status evaluation is of major importance and helps to access the impact of PEI in patients not only by the time of diagnosis but also monitoring disease development and the efficacy of treatment.

Pancreatic endocrine insufficiency

Overt diabetes *mellitus* (DM) usually occurs late in CP. Around 60-75% of CP patients and up to 90% of calcifying CP patients have DM and those with alcoholic intake will develop insulin insufficiency earlier [1]. DM may also be the first manifestation of painless forms of pancreatitis (20%) [10].

As fibrosis increases, islet cell injury with beta cell mass reduction leads to impairment of insulin secretion [11]. As type 1 DM, CP-related diabetes (type 3)

usually requires insulin therapy. However, the major difference between them is the simultaneous alfa cell reduction that occurs in type 3 DM, leading to glucagon impairment and, therefore, increased risk of hypoglycemia both, spontaneous and treatment related [12, 13].

CP-related DM has the same diagnostic criteria as type 1 or 2:

// Fasting plasma glucose ≥126 mg/dL (at least 8 hours fasting).

// Oral glucose tolerance test at 2 hours ≥200 mg/dL.

// HbA1c ≥6.5%.

Treatment with insulin is the standard of care. Metformin is sometimes used as a first approach in patients with a high ratio insulin/C-peptide, HbA1c ≤7%, high body mass index and family history of DM.

As diabetes progresses, neuropathy contributes to abdominal features like cramps and diarrhea. Diabetic ketoacidosis and nephropathy are rare.

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3.2. Functional tests

Joana Rita Carvalho and Teresa Antunes

Pancreatic juice consists of water and bicarbonate (both secreted by ductal cells) and enzymes – amylase, lipase, trypsin(ogen), chymotrypsin(ogen), (pro) elastase, (pro)carboxypeptidase, fosfolipase A2 and carboxylesterase- secreted by acinar cells.

Pancreatic exocrine insufficiency (PEI) can be defined as an inadequate pancreatic enzyme activity due to insufficient enzyme production, insufficient enzyme activation or early enzyme degradation.

In chronic pancreatitis (CP), subtle functional changes occur at early stages of fibrosis, namely, impairment of bicarbonate secretion (which plays an important role buffering gastric acid in the duodenum), thus providing stability to enzymes (mainly lipase), which rapidly degrades when pH is below 4. PEI develops silently in the early stages of CP and increases with disease duration. Approximately 50% of patients will develop symptoms due to PEI by 10 to 15 years after onset of the disease [1, 2].

Diagnosis of pancreatic exocrine insufficiency

In order to assess pancreatic function, direct and indirect methods are used nowadays. In cases of CP clinical suspicion, a functional evaluation should be performed because even mild-to-moderate insufficiencies can disturb the digestive process and lead to clinical implications.

Deficiencies of several nutrients have been demonstrated in CP even before steatorrhea is installed [3]. Direct tests estimate the products released in pancreatic secretion (bicarbonate and enzymes). Indirect tests evaluate the pancreatic function through the presence or quantification of pancreatic enzymes in serum or stool or even by the presence of labeled carbon dioxide (CO_2) in exhaled air [3].

DIRECT TESTS

SECRETIN-PANCREOZYMIN TEST (SECRETIN CHOLECYSTOKININ TEST)

A double lumen nasoduodenal tube is placed for constant aspiration of gastric fluids and for collection of duodenal samples every 10 minutes, for 1 hour after stimulation with secretin alone or combined with cholecystokinin (CCK) or cerulein. The secretin CCK

DIRECT TESTS
1. Secretin-pancreozymin test 2. Endoscopic secretin / pancreatic function test
INDIRECT TESTS
1. Fecal tests: Fecal elastase Fecal chymotrypsin Fecal fat content **2. Breath test** ^{13}C, ^{14}C, H_2 breath test **3. Urine tests** Pancreolaury test NBT-PABA test (bentiromide test) **4. Serum tests** Pancreolauryl test Pancreatic enzyme **5. Secretin-enhanced magnetic resonance cholangiopancreatography**

TABLE 1
SUMMARY OF DIAGNOSTIC TESTS OF PANCREATIC EXOCRINE INSUFFICIENCY

test protocol differs among centers. Different doses of stimulation are used, bolus or continuous IV infusion, different quantifications of the samples (regarding volume, bicarbonate concentrations and enzyme quantification amylase and/or lipase or proteases).

The analysis of bicarbonate and enzyme concentration allows a scale of severity as mild, moderate or severe dysfunction [4]. Although, this test is considered the gold standard (sensitivity and specificity >90%) as it measures directly the pancreatic secretion after stimulation, it has been progressively abandoned, because it is an invasive, time consuming, non-standardized and expensive method [4].

ENDOSCOPIC SECRETIN / PANCREATIC FUNCTION TEST

In order to avoid problems associated to the standard test (intubation, duration and/or standardization) a variant of the previous secretin test was developed using an upper endoscope (standard or thinner) to collect samples, instead of the gastroduodenal tube. Sedation is used for patient comfort and does not significantly affect pancreatic secretion [5]. In the standard endoscopic secretin / pancreatic function test (ePFT), 5 sample collections (3-5 mL) are executed (baseline and every 15 minutes for one hour) after stimulation with 0.2 µg/kg of secretin.

A 2-sample ePFT is currently used. Samples are collected at 30 and 45 minutes after secretin administration. This method has a high sensitivity for detecting PEI [6].

INDIRECT TESTS

Comparing to direct tests, indirect tests of pancreatic exocrine function are less sensitive and less specific but cheaper and easier to administer [7]. The basis of indirect tests is to detect alterations due to loss of pancreatic exocrine function and can be divided into 4 categories: fecal, breath, urinary and blood tests [7]. They are best used to quantify the degree of insufficiency in already-established late CP [8] and generally should be accompanied by cross sectional computed tomography or magnetic resonance imaging to rule out malignancy [9].

FECAL TESTS

Three-day fecal fat test

It is considered the gold standard to diagnose steatorrhea and the most commonly method used is the Van the Kamer method [10]. It consists in a diet containing 100 g of fat (for adults) for 3-5 days; then, stools are collected and pooled for analysis, and the

coefficient of fat absorption is measured [10]. Steatorrhea is present if more than 7% of ingested fat is excreted [7]. It has 92% of sensibility but only 42% specificity for PEI, as it does not distinguish between pancreatic and non-pancreatic causes of PEI [11].

Fecal elastase and chymotrypsin

Fecal elastase is a pancreatic specific protease, which is not degraded by the intestine, and is concentrated 5 to 6 times higher in stool compared to pancreatic secretion [12]. A low FE-1 concentration of <200 µg/g suggests PEI, whereas <100 µg/g suggests severe PEI [7]. Classic false-positive fecal elastase measurements (low levels) occur in small bowel bacterial overgrowth and watery stool. Classic false-negative serum trypsin measurements (normal/high levels) occur when performed in the setting of acute pancreatic inflammation [9]. Its sensitivity varies from 0–63% in mild-to-moderate PEI to 77–100% in moderate-to-severe PEI, while its specificity ranges from 80–95% in mild-to-moderate PEI to 76–100% in moderate-to-severe cases [13]. A polyclonal fecal elastase may be a better test [13], however, the monoclonal assay is currently better standardized [9]. Fecal chymotrypsin is no longer employed because the fecal elastase test has been proved to have more sensitivity and specificity [7].

Microscopic examination of stools for fat droplets

It works just as a screening test that can be performed before additional tests. It consists of microscopic stool examination in order to detect fat globules. Sudan III stain helps to visualize neutral fat globules [7].

BREATH TESTS

Ingested lipids are mainly hydrolyzed by pancreatic lipases in the small intestine, absorbed as free fatty acids and monoglycerides, and transported to the liver, where oxidative metabolism liberates CO_2 [7]. Radiolabeled carbon breath tests samples are taken before and after a test meal containing ^{13}C-labeled substrate. The most widely used test is the ^{13}C-labeled mixed triglyceride breath test [14]. It involves the ingestion of 250 mg of 2-octanoyl (1-13C)-1.3 distearoyl glycerol (Euriso-top, Saint-Aubin, France) with 16 g of fat. This substrate is digested by lipase, releasing ^{13}C-labeled octanoic acid, which is then absorbed and metabolized to form $^{13}CO_2$, and ultimately released in expired breath. Breath samples are collected at 15 minute intervals for 6 hours [14]. Dominguez-Muñoz, ***et al.*** [14] showed that this might be an accurate and alternative method to the quantitative fecal fat test to assess the effect of enzyme therapy on fat digestion and the correction of fat malabsorption during therapy. Its limitations are its poor sensibility in the absence of steatorrhea and inability to differentiate between pancreatic and non-pancreatic causes of fat malabsorption [7].

URINE TESTS

Urine tests use non-absorbable substrates which are specifically cleaved by pancreatic enzymes, conjugated in liver and excreted in urine [7]. The 2 most commonly used substrates are bentiromide and fluorescein dilaurate; after its ingestion urine is collected and the substrate is measured [7, 15]. However, these tests are poorly used as they have been replaced by the fecal elastase and direct tests which have better specificity and sensitivity [7].

SERUM TESTS

Trypsin is exclusively synthesized by the pancreas and released into the blood as proenzyme trypsinogen [7]. Blood tests to evaluate PEI consist on the measurement of serum immunoreactive trypsinogen [7] and have been validated to PEI in the context of cystic fibrosis [16]. Serum trypsinogen levels below 20 ng/mL are reasonably specific for PEI in patients over 7 years of age, however its fluctuating pattern during the first decade of life in children with cystic fibrosis implies the need for serial measurements [7, 16].

SECRETIN-ENHANCED MAGNETIC RESONANCE CHOLANGIOPANCREATOGRAPHY

Secretin-enhanced magnetic resonance cholangiopancreatography (s-MRCP) is an image method of indirectly access PEI. It adds functional and anatomic information about the pancreatic ducts and pancreatic exocrine reserve. The basic principle underlying MRCP is to produce high contrast resolution between the fluid-filled pancreatic ducts and the adjacent tissues which result is an image that resembles those obtained by means of direct cholangiography in a totally non-invasive manner [17]. The exogenous administration of secretin during MRCP image acquisition improves pancreatic duct visualization because it stimulates both pancreatic gland and ducts, working as a contrast agent [18]. In other words, in severe CP, in which the inflammation/fibrosis process is more advanced, it is a non-invasive method of assessing the pancreatic exocrine reserve by analyzing the amount of pancreatic juice collected within the duodenal lumen which will be significantly reduced [17]. In adults, secretin is administered in a dose of 1 clinical unit per kg of body weight (0.7–1 mL/10 kg

of body weight), which is considered as the standard dose, responsible for a maximal stimulation of the exocrine pancreas [17]. Matos ***et al.*** [19] evaluated 10 healthy volunteers and 13 patients with pancreatic disease who were submitted to s-MRI; the mean duodenal filling score was significantly lower in patients with reduced exocrine function (six patients) than that in the volunteers ($p<0.0001$), concluding that the use of dynamic MR pancreatography with secretin stimulation may be useful for detecting reduced pancreatic exocrine reserve. In this context, s-MRI may be useful in the diagnosis of pancreato-biliary abnormalities related to recurrent episodes of pancreatitis (such as pancreas ***divisum***, sphincter of Oddi dysfunction, santorinicele, annular pancreas) and in CP with PEI [17].

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3.3. Imaging modalities

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In chronic pancreatitis (CP) recurrent inflammatory episodes result in replacement of pancreatic parenchyma by fibrous connective tissue [1-4]. This fibrotic reorganization of the pancreas leads to several parenchymal and ductal changes that can be detected by imaging modalities. In addition, characteristic complications may arise, such as pseudocysts, obstruction of the pancreatic and/or biliary duct, obstruction of the duodenum, vascular complications and pancreatic carcinoma that can also be detected by imaging modalities.

The diagnosis of CP is based on clinical history, imaging modalities and pancreatic function testing. Due to the insufficient correlation of these three diagnostic pillars, they should be used in a complementary way [1-4]. In any case, imaging modalities are indispensable for the diagnosis of CP and its complications. In fact, in most patients presenting with indicators suggestive of CP, the imaging modalities will establish the diagnosis by demonstrating unequivocal pancreatic changes. Nevertheless, they may also show no or equivocal pancreatic changes that should be always integrated with clinical history and pancreatic function testing, since that changes may be related to early CP or not be related to CP at all.

Current imaging modalities for the diagnosis of CP include transabdominal ultrasound (US), computed tomography (CT), magnetic resonance imaging with cholangiopancreatography (MRI+MRCP), endoscopic

ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP) [1-4]. They mainly differ in terms of diagnostic accuracy for parenchymal and ductal changes (especially in early CP) and complications of CP and their invasiveness. This section aims to describe how imaging modalities can be used in the process of evaluating a patient with suspected CP.

Transabdominal ultrasound

The diagnosis of CP by US relies on changes in morphology of the pancreas, easily detected in the setting of advanced disease, but challenging in early disease [1, 4, 5]. The classic sonographic findings of CP are pancreatic and/or intraductal calcifications. These calcifications, that are pathognomonic for CP in the appropriate clinical context, are seen as multiple echogenic in roughly 40% of patients with advanced CP. These foci may or may not shadow-based on their size and may show color Doppler twinkling artifact. Other typical sonographic signs of advanced CP are duct caliber abnormalities, i.e. a dilated and irregular pancreatic duct. Late findings seen on ultrasound also include alterations in the size and echogenicity of the pancreas, but these findings are non-specific, since they can also be found in healthy elderly subjects. US can also detect CP complications such

GRADE	US	CT/MRI+MRCP	ERCP
0	normal organ, duct <2 mm, regular contour	none	no pathological alterations on good visualization of pancreatic duct system
1	echo-dense gland contour, gland enlarged (up to 1.5-fold), duct <3 mm, lobular honeycomb appearance	not possible to demarcate duct system on CT/MRCP using current methods	<3 abnormal side branches, main duct normal
2	contour irregularities, irregular hyperechoic main pancreatic duct >3 mm, lobular texture with echo-dense septations	≥2 of the following changes: pancreatic duct between 2 and 4 mm in the pancreatic body; mild pancreatic enlargement; heterogeneous parenchymal structure; small cystic changes (<10 mm); duct irregularities; pathological side branches >3	>3 abnormal side branches, main duct normal
3*	as in 2, plus cysts, focal calcifications	all changes named under 2 plus pathological main duct (>4 mm)	≥3 abnormal side branches plus abnormal main pancreatic duct
4*	as in 3, plus duct stones, duct obstruction, tumorous enlargement of the gland >2-fold, splenic vein thrombosis	one of the changes named under 2 or 3 plus ≥1 of the following: cystic structures >10 mm; parenchymal calcifications; intraductal filling defects (calcifications); duct obstruction (strictures); major duct irregularities	as in 3, plus cysts, duct calculi, duct obstruction (stricture), involvement of adjacent organs

TABLE 1
CAMBRIDGE CLASSIFICATION FOR TRANSABDOMINAL ULTRASOUND (US), COMPUTED TOMOGRAPHY (CT), MAGNETIC RESONANCE IMAGING WITH CHOLANGIOPANCREATOGRAPHY (MRI+MRCP) AND ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY (ERCP) FINDINGS IN CHRONIC PANCREATITIS
Adapted from Hoffmeister *et al.* [2]
*Cambridge grades 3 and 4 are considered diagnostic of chronic pancreatitis.

as pseudocysts, biliary dilatation and splenic vein thrombosis. In early CP, there are no (or only subtle) morphological changes that cannot be detected by conventional US. The Cambridge classification can be used to grade the US findings [1, 2, 4, 6] - table 1.

In summary, US is frequently the first line imaging modality used in patients with abdominal pain and the suspicion of CP. This is because it is a non-invasive, inexpensive and rapid method of evaluating morphological changes in the pancreas, is readily available in most facilities and can easily be repeated without the inherent risks of radiation and contrast media of other techniques. However, apart from the low sensitivity and specificity of the majority of US findings in the diagnosis of CP, US has considerable limitations that reduce its diagnostic utility such as operator-dependency and obscured visualization of the pancreas, for example, due to obesity or intestinal gas.

Computed tomography

CT has seen profound improvements over the last 3 decades (such as multidetector technology, multiplanar reconstruction images and multiphase imaging with contrast) that undoubtedly improved its sensitivity in the diagnosis of CP [4]. The diagnosis of CP by CT relies on changes in morphology of the pancreas, easily detected in advanced CP, but hardly detected in early disease [1, 4, 5]. The classical CT findings in CP are dilatation of the pancreatic duct, pancreatic calcifications and parenchymal atrophy. The main pancreatic duct is classically beaded and irregular; however, the main duct may also be regularly contoured. CT examination is considered the most appropriate method for identifying pancreatic calcifications. Nevertheless, very small calcifications may be obscured by pancreatic parenchymal contrast enhancement and thus pancreatic CT should include a non-contrast-enhanced phase in order to depict these calcifications. Normal pancreatic morphology as well as pancreatic enlargement may also be observed on CT imaging in CP, making the diagnosis particularly difficult in certain population of patients. Additionally, while pancreatic atrophy is visualized in a large proportion of patients with CP, this is not a specific finding and can also be seen with normal aging. The Cambridge classification can be used to grade the CT findings [1, 2, 4, 6] - table 1.

CT is especially helpful in identifying complications of CP, including pseudocysts, portosplenic venous thrombosis, collaterals and arterial pseudoaneurysms, and pancreatico-pleural fistulas [1, 4, 5]. CT may be also useful in the differential diagnosis between mass-forming pancreatitis from pancreatic cancer [1]. Features that favor CP are intraductal or parenchymal calcifications, lack of obstructing mass, irregular dilatation of the pancreatic duct and relatively limited atrophy of the gland. The presence of a “duct-penetrating” sign, that is, a dilated duct or branches which penetrate an apparent mass, favors CP. Features favoring cancer include pancreatic duct dilatation with associated mass at the site of obstruction, atrophy of the pancreas, vascular invasion and metastases. Nevertheless, it should be emphasized that, like with all imaging modalities, the ability of CT to detect carcinoma in patients with CP is significantly reduced.

In summary, CT is considered for many as the best initial imaging test in the workup for CP since it is widely accessible, allows for comprehensive detailed evaluation of the pancreas and it is especially useful in detecting changes seen in advanced disease and complications of CP. Moreover, it can quickly assess extrapancreatic pathology that may explain various presentations mimicking CP. It has, however, two important limitations: it has significant limitations in evaluation of pancreatic ductal anatomy as well as assisting in diagnosis of early CP and it poses the risks of radiation.

Magnetic resonance imaging with cholangiopancreatography

This technique has emerged as a reliable tool for accurately characterizing pancreatic pathologies due to its superior soft-tissue and contrast resolution [5, 7]. This results from the multiplicity of pulse sequences with different tissue contrast properties that are used in MRI [5]. MRI+MRCP is highly sensitive and specific to make the diagnosis of CP by evaluating both parenchymal and ductal changes, especially in patients with more advanced CP [1, 4, 5]. Parenchymal changes that are visualized via MRI include pancreatic atrophy, depressed T1 signal, irregular contour of head or body, heterogeneous parenchyma and delayed gadolinium enhancement of the pancreas after administration. Ductal changes include intraductal filling defects often indicative of calculi, main pancreatic duct dilation, side branch dilation and irregular duct contour. While there are no standardized criteria for diagnosing CP with the use of MRI+MRCP, the Cambridge classification may be adapted to grade MRI+MRCP findings [1, 2, 4] - table 1.

One of the challenges of MRI+MRCP in the diagnos-

tic evaluation of CP is its relatively low sensitivity in early CP, since subtle changes in the main pancreatic duct and the side-branches cannot be identified as easily with MRCP as with ERCP. Secretin-enhanced MRCP (s-MRCP) has been shown to ameliorate this limitation, increasing the diagnostic potential of MRCP in the evaluation of patients with known/suspected CP [3, 8]. This method uses IV secretin (that stimulates pancreatic exocrine function and increases fluid excretion via the main pancreatic duct) and subsequently observes the T2 intensity changes seen within the pancreatic duct. It is useful in the evaluation of CP with MRCP for two main reasons: 1) it enhances visualization of the main pancreatic duct and abnormal side-branches compared to conventional MRCP, increasing the overall sensitivity for the detection of ductal changes of CP [9]; 2) it may quantify exocrine function (through evaluation of pancreatic duct compliance and pancreatic duct flow rate) which correlates well with the severity of pancreatitis [8]. Importantly, several studies have shown that patients with early CP may have completely normal conventional MRI+MRCP and only the secretin stimulation will depict mild ductal changes [1, 4, 5]. Nevertheless, the use of secretin is limited by its high cost.

MRI+MRCP has a high sensitivity and specificity in the differential diagnosis between mass-forming CP and pancreatic cancer [10]. This is largely based on the same findings described above in the CT section, especially on the "duct-penetrating" sign. However, this does not apply when a carcinoma develops in the presence of CP. In this case, like with all imaging modalities, the sensitivity and specificity is significantly reduced and inferior to that documented for EUS-guided tissue acquisition. Some future MRI applications are on the horizon that may have immediate impact on the way we image patients with CP [7]. Diffusion-weighted imaging, perfusion MRI and MRI spectroscopy may all increase the role of MRI in the diagnosis of early CP and/or in the differential diagnosis between mass-forming pancreatitis and pancreatic cancer.

In summary, MRI+MRCP is a great tool to detect ductal and parenchymal changes and complications in CP both at "baseline" or after stimulation with secretin. Nevertheless, it still has relatively low sensitivity in early CP (although this may increase with the use of secretin). Additionally, it is more expensive, time-consuming and patient collaboration-dependent and less available than CT.

Endoscopic ultrasound

Due to its superior spatial resolution, EUS is considered the most sensitive imaging technique for the diagnosis of CP, mainly during the early stages of the disease. It is in this subset of patients where EUS has the most potential to assist in diagnosis, as it is rarely needed for diagnostic purposes in advanced CP.

Like MRI+MRCP, EUS evaluates both parenchymal and ductal changes of CP. A total of 9 EUS criteria (4 parenchymal and 5 ductal) have been proposed by the International Working Group in the diagnosis of CP [11] - table 2.

To date, there is no optimal EUS cut-off for establishing a diagnosis of CP. However, a cut-off of 5 criteria is often used [1-3, 5]. The presence of 5 or more findings provides a definitive diagnosis of CP whereas 2 or less effectively rules out this disease. Patients with 3-4 criteria have an indeterminate diagnosis and should be thoroughly worked up further with pancreatic function testing. The 9 criteria have been linked to distinct histological changes noted from specimens collected after EUS evaluation [12] - table 2. Given the lack of standardization across EUS interpretation in the

PARENCHYMAL CRITERIA	HISTOLOGIC CORRELATE	DUCTAL CRITERIA	HISTOLOGIC CORRELATE
Hyperechoic foci Hyperechoic strands Lobular contour Cysts	Focal fibrosis Bridging fibrosis Interlobular fibrosis Cyst/pseudocyst Calcified stones	Main duct dilation (mm) Duct irregularity Hyperechoic margins Visible side branches Stones	>3 head, >2 body, >1 tail Foca dilation/narrowing Periductal fibrosis Side branch dilation Calcified stones

TABLE 2
ENDOSCOPIC ULTRASOUND CRITERIA FOR CHRONIC PANCREATITIS AND HISTOLOGICAL CORRELATES

CRITERION		DEFINITION	CRITERIA WEIGHTING
Hyperchoic foci	with shadowing	Echogenic structures >2 mm in both length and width that shadow	Major A
	without shadowing	Same as above but no shadowing	Minor
Lobularity	with honeycombing	Well-circumscribed, >5 mm structures with enhancing rim and relatively echo-poor center, contiguous >3 lobules	Major B
	without honeycombing	Same as above but non-contiguous lobules	Minor
Stranding		Hyperechoic lines of >3 mm in length in at least 2 different directions with respect to the imaged plane	Minor
Cysts		Anechoic, rounded/elliptical structures with or without septations	Minor
MPD calculi		Echogenic structure(s) within MPD with acoustic shadowing	Major A
Irregular MPD contour		Uneven or irregular outline and ectatic course	Minor
Dilated side branches		Three or more tubular anechoic structures each measuring >1 mm in width, budding from the MPD	Minor
MPD dilation		≥3.5-mm body or ≥1.5-mm tail	Minor
Hyperechoic MPD margin		Echogenic, distinct structure greater than 50% of entire MPD in the body and tail	Minor

TABLE 3
ROSEMONT CRITERIA FOR CHRONIC PANCREATITIS
MPD: main pancreatic duct

context of CP, the Rosemont criteria were developed from the consensus opinion of 32 endosonographers [13] - table 3. However, this classification is more complex and does not improve the diagnostic value of the standard criteria. While these criteria are helpful in the workup of CP, some of the EUS findings have low specificity since they may also be the result of normal anatomic variants, or of non-diagnostic asymptomatic fibrosis in the absence of endocrine or exocrine dysfunction as it is seen in alcoholism, advanced age,

male gender, obesity and cigarette smoking [14].

Like other imaging modalities, EUS is also able to detect multiple complications of CP, in particular pancreatic cancer. Although there is no clear consensus on whether and how to conduct pancreatic cancer screening in CP, many centers recommend the use of EUS, based on its ability to identify small pancreatic masses, even so this ability is reduced in the presence of CP.

EUS-guided tissue acquisition is an essential tool in the differential diagnosis between mass-forming CP and pancreatic cancer [3]. In fact, EUS-guided tissue acquisition is considered as the most reliable procedure for detecting pancreatic malignancy in patients with or without CP, although in CP the sensitivity decreases from 80-95% to 50-75% [3]. There is also a probability of false negatives (between 5-10%) and thus in patients with suspected operable pancreatic cancer in imaging modalities surgery is recommended even without prior cytological confirmation. New EUS imaging techniques, such as elastography (E-EUS) and contrast-enhanced harmonic EUS (CEH--EUS) have also been proposed to increase the accuracy of EUS in the differential diagnosis between mass-forming CP and pancreatic cancer, not only by allowing better imagiological characterization of the mass, but also by directing EUS-guided tissue acquisition. Although two recent meta-analysis [15, 16] have demonstrated that CEH-EUS and E-EUS are reliable techniques for the characterization of solid pancreatic masses, most studies were unicentric and included low number of patients with CP, which may limit the reproducibility of data in routine practice [16, 17]. Several computer-aided diagnosis methods for E-EUS and CEH-EUS may reduce various biases and increase the accuracy of EUS in this setting, but their role in the characterization of solid pancreatic lesions in patients with CP is still unclear. Thus, although E-EUS and CEH-EUS may deliver accurate information and may be useful complementary tools for EUS-guided tissue acquisition in experienced hands, their role in this setting needs to be assessed further in future clinical trials.

In summary, EUS is the most sensitive imaging technique for the diagnosis of CP, mainly during the early stages of the disease, and its specificity increases with increasing diagnostic criteria. Additionally, EUS-FNA (fine needle aspiration) is the most accurate technique in the differential diagnosis between mass-forming CP and pancreatic cancer and in the early detection of malignancy in patients with known CP. However, there are important limitations including invasiveness, availability, operator–dependency and low specificity of some findings. Further studies are needed to refine the definitions of EUS criteria of CP, to determine the relative predictive value of each criteria and its relation to aging, obesity, and smoking, to establish an ideal threshold number of criteria and to increase reproducibility in image interpretation and improved interobserver agreement.

Endoscopic retrograde cholangiopancreatography

Following the advent of CT, MRI+MRCP and EUS, the use of ERCP in the management of CP is typically limited to therapeutic interventions rather than purely diagnostic. Historically, specific findings described in CP by a retrograde pancreatogram obtained during ERCP include the main pancreatic duct caliber and contour, clear definitions of its side branches, intraductal filling defects, strictures and cavity formation. The Cambridge criteria were an attempt to standardize interpretations of various pancreatogram findings [6] - table 1.

Although ERCP is sensitive for detection of changes in the pancreatic duct, there are several drawbacks when used for the diagnosis of CP. First, like EUS, it is operator-dependent and prone to interobserver variability. Next, it does not provide assessment of the classic parenchymal CP changes. Moreover, it is the most invasive diagnostic modality and carries post-procedural risks, most notably, post-ERCP pancreatitis. Finally, other potential confounders to interpretation of pancreatograms include age-related ductal changes and post-acute pancreatitis ductal changes which are indistinguishable from ductal changes related to CP. For these reasons, ERCP should be used for diagnosing CP only when all other imaging modalities have been exhausted.

How to use imaging modalities for CP diagnosis?

A recent review and meta-analysis evaluated the sensitivity and specificity of the different imaging modalities for CP diagnosis [17]. In this meta-analysis, authors estimated the diagnostic accuracy for each imaging

CLINICAL HISTORY, PHYSICAL EXAM, ROUTINE LAB TESTS, CONSIDER INDIRECT (NON-INVASIVE) PANCREATIC FUNCTION TESTING

PANCREATIC CHRONIC PANCREATITIS AND/OR MAGNETIC RESONANCE IMAGING WITH CHOLANGIOPANCREATOGRAPHY ± SECRETIN
Chronic pancreatitis diagnostic criteria: Cambridge grade 3 or 4
If results are equivocal, proceed to the next step

ENDOSCOPIC ULTRASOUND ± ELASTOGRAPHY, CONTRAST-ENHANCEMENT, TISSUE ACQUISITION
Chronic pancreatitis diagnostic criteria: ≥5 standard endoscopic ultrasound criteria
If results are equivocal, proceed to the next step

DIRECT (INVASIVE) PANCREATIC FUNCTION TESTING
Chronic pancreatitis diagnostic criteria: peak [bicarbonate] <80 mEq/L
If results are equivocal, proceed to the next step

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY
Chronic pancreatitis diagnostic criteria: Cambridge grade 3 or 4
If results are equivocal, consider clinical monitoring and repetition of previous test

FIGURE 1
ALGORITHM APPROACH TO DIAGNOSIS OF CHRONIC PANCREATITIS
Adapted from Conwell *et al.* [1]

modality independently as well as performed head to head comparisons when possible and came to the following conclusions: EUS, ERCP, MRI+MRCP and CT all have comparable high diagnostic accuracy in the initial diagnosis of CP; EUS and ERCP outperform the other imaging techniques and US is the least accurate; the choice of imaging modality can therefore be made on the basis of invasiveness, local availability, experience and costs.

As diagnostic sensitivity of CT and MRI+MRCP is not significantly lower than that of ERCP and EUS, and specificity is comparable, these non-invasive modalities are a likely first choice in patients with suspected CP. If the results are normal or equivocal but still there is a high suspicion of CP, the next choice should be EUS mainly due to its high accuracy in general and for early CP in particular. Due to its invasiveness and risks, ERCP should be the last choice when all other imaging modalities and pancreatic function tests have been exhausted. Equivocal results of imaging modalities should always be interpreted according to clinical presentation and pancreatic function tests. Monitoring of symptoms and repetition of imaging modalities should also be considered. We propose an algorithm approach to diagnosis of CP that is presented in figure 1.

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4

TREATMENT

4.1. Medical treatment

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Medical treatment of chronic pancreatitis (CP) includes lifestyle modification, nutrition, exocrine and endocrine pancreatic insufficiencies correction and pain management.

Lifestyle modification

Abstinence from alcohol and tobacco are essential and mandatory components of medical guidance. Alcohol abstinence has a significant effect on endocrine pancreatic function [1]. There is also a maintained deterioration in pancreatic exocrine function, both in patients who stop alcohol and in those who continue. The deterioration, however, is significantly less marked in patients who stop drinking alcohol than in those who continue [2]. Alcohol intake, even less than 50 g/day, induces earlier disease characterized by more frequent severe pain, pancreatic calcifications and complications. Intake of large amounts of alcohol (≥50 g/day) accelerates calcification and reduces life expectancy [3]. In fact, the cumulative 5-years mortality rate has been demonstrated to be higher in alcoholic than idiopathic pancreatitis (26% vs 10%, $p<0.01$) [4].

Tobacco smoking is associated with earlier diagnosis of chronic alcoholic pancreatitis and earlier appearance of calcifications and diabetes [5, 6]. In fact, it is an independent risk factor for pancreatitis and accel-

erates the course of CP in a dose-dependent fashion, apart from alcohol intake [7]. Even for idiopathic CP, smoking has been extensively demonstrated as an independent risk factor [8]. Physicians often underrecognize smoking as a CP risk factor as demonstrated in the North American Pancreatitis Study 2 (which evaluated 535 patients with CP) where physicians cited smoking as a risk factor in only 45% of CP patients who self-reported as ever-smokers [9]. Tobacco cessation appears to be associated with even more benefits as it also reduces the risk of secondary pancreatic carcinoma besides other tobacco induced pathologies. The International Pancreatic Cancer Case–Control Consortium (PanC4, which included 6507 pancreatic cases and 12 890 controls) demonstrated that compared with never-smokers, the OR was 1.2 for former smokers and 2.2 for current cigarette smokers, with a significant increasing trend in risk with increasing number of cigarettes among current smokers (OR = 3.4 for ≥35 cigarettes per day). Risk increased in relation to duration of cigarette smoking up to 40 years of smoking (OR = 2.4). No trend in risk was observed for age at starting cigarette smoking, whereas risk decreased with time since cigarette cessation, reaching the level of never-smokers approximately 20 years after quitting [10].

Nutrition

Malnutrition is common in CP, which is aggravated because up to 50% of patients have increased resting energy expenditure, and its severity is a major predictive factor of complications and outcome. Although reduced fat diet may permit partial symptoms control, fat content should be normal (30% of total energy intake) to prevent malnutrition. In fact, the ESPEN (European Society for Clinical Nutrition and Metabolism) advocates a normal diet supplemented by pancreatic enzymes for the vast majority of patients [11]. Ten to 15% will require nutritional supplements and only 5% tube feeding. Deficiencies in vitamins A, D, E and K (secondary to steatorrhea), and in vitamin B12, calcium, magnesium, zinc, thiamine and folic acid can also occur, so they should be considered and supplemented if necessary [11]. A cross-sectional study revealed deficiencies in vitamins A, D, E and K in 3, 53, 10, and 63% of patients with CP, respectively. Osteopenia and osteoporosis were observed in 45% and 10% [12].

Azotorrhea, from protein malabsorption, develops several years after steatorrhea and is clinically less significant because protein digestion is initiated by gastric proteases and continued by intestinal brush border peptidases. However, this problem may be underestimated because there is fewer data on physiological malabsorption of proteins as it has been difficult to differentiate between dietary and endogenous proteins. Moreover, protein maldigestion and malabsorption are measured in the feces while there is a fast colonic fermentation of any unabsorbed protein [13]. Nevertheless, most pancreatic enzyme supplementation include proteases.

A pilot study involving 8 CP patients tested an enteral formulation containing medium-chain triglycerides, which have a lipase and bile independent absorption. The average improvement in pain scores from baseline to the conclusion of the study was 61.8% and there was a minimal increase in plasma cholecystokinin (CCK) levels in contrast to high-fat meals and standard enteral feedings that contain long-chain triglycerides which stimulate CCK release and pancreatic secretions and may worsen the pain associated with CP [14].

Exocrine pancreatic insufficiency

In 2009, a Cochrane systematic review that evaluated 10 trials about efficacy of pancreatic enzyme replacement therapy (PERT) in patients with CP was inconclusive; therefore, better quality and adequately powered studies for a definitive conclusion were needed. Nonetheless, some individual studies reported a beneficial effect of PERT over placebo in improving pain, incidence of steatorrhea and analgesic consumption but studies' results could not be pooled for these outcomes [15].

In 2017, a more recent systematic review and meta-analysis of 17 randomized controlled trials of PERT demonstrated a statistically significant superiority of PERT versus placebo and versus baseline in terms of coefficient of fat absorption, coefficient of nitrogen absorption, reduced fecal fat and nitrogen excretion, fecal weight and abdominal pain. The follow-up studies also demonstrated improvement of serum nutritional parameters, gastrointestinal symptoms and quality of life. All these gains were achieved without significant adverse events [16]. Therefore, PERT is recommended in patients with significant steatorrhea (>15 g/day), symptomatic steatorrhea (diarrhea, weight loss or other signs of malnutrition). The benefit in treating asymptomatic patients with less severe steatorrhea (from 7.5 to 15 g/day) is not clear [17]. The United European Gastroenterology (UEG) guidelines also recommend PERT for patients with CP and PEI in the presence of clinical symptoms or laboratory signs of malabsorption, with a high level of evidence [18].

Typically, steatorrhea develops when the pancreatic lipase production falls to <10% of normal. With the objective of controlling this, a minimal dosing of 25 000 - 50 000 IU (International Units)/Ph. Eur. U (Pharmacopoeia European Units) of lipase per meal is required (providing approximately 10% of the physiologic pancreatic secretion). One capsule should be swallowed at the beginning of the meal (including small meals or snacks) and for major meals a second dosage should be administered during the meal to ensure an adequate release of enzymes throughout digestion. Patients who do not respond adequately to PERT should initiate a proton pump inhibitor (PPI), which is obligatory from the initiation of therapy in non-enteric coated enzymes. Increasing of the dose, if necessary, should be slow and accompanied by careful monitoring and symptom checking. The most recent and well-designed RCTs have shown the efficacy of PERT with enteric-coated minimicrospheres at a dose ranging from 40 000 – 80 000 IU of lipase per main meal, and half that dose per snack [18]. In general, dosage should not exceed 10 000 U lipase/kg of body weight per day. Failure to improve steatorrhea after dose optimization and PPI should lead to investigate low patient compliance, intestinal bacterial overgrowth (may be present in a third of patients) [19], intestinal infections or other disorders associated with malabsorption [13].

There is a considerable variation in different countries in PERT dosage, enteric-coating, formulations (granules, tablets, microspheres, minimicrospheres or capsules), kinetics of duodenal lipase release and bioequivalence [20]. The optimal regimens of PERT and comparisons of the different formulations in its long-term effects on nutrition are not yet determined, lacking further studies. However, high-dose or enteric-coated enzymes showed a trend to greater effectiveness than low-dose or non-coated [16]. In Portugal, for the treatment of PEI, there are two formulations of enteric-coated, gastro-resistant capsule approved by Infarmed (National Authority for Medicines and Health Products). These enteric--coated capsules of minimicrospheres contain (amylase 8000 U + lipase 10 000 U + protease 600 U and amylase 18 000 U + lipase 25 000 U + protease 1000 U respectively under the trademark of Kreon® and Kreon 25 000®). There is one low-dose, non-enteric tablet formulation (amylase 6 000 U + lipase 6 000 U + protease 400 U + dimeticone 80 mg under the trademark of Pankreoflat®) but has not an approved indication for the treatment of PEI [21].

The main objective of PERT is to avoid symptoms associated with exocrine insufficiency (diarrhea, weight loss, bloating) and normalize nutritional status. This should be assessed by evaluating body weight and weight loss, considering several factors such as nutrient intolerance, dietary intake and restrictions, symptoms of specific nutrient deficiencies (hair loss, glossitis, dermatitis, paresthesias), anthropometry (body mass index and muscular arm circumference), biochemical tests (albumin, transferrin, liposoluble vitamins, cholesterol), lymphocyte count, muscle function (hand grip) and nutritional indexes. Alcohol or drugs abuse should also be considered. The response to PERT can also be objectively measured with ^{13}C-mixed triglyceride breath test or the coefficient of fat absorption (CFA quantification). After symptom control, the chosen test should be repeated with increasing PERT doses until it attains a normal value. This approach is associated with a normalization of the body mass index and the nutritional status of patients. However, for most patients, symptoms and nutritional status are sufficient for monitoring response to treatment [17].

Endocrine pancreatic insufficiency

Depending on the cohort, diabetes *mellitus* has been described in 26-80% of CP patients. In this context, diabetes is categorized as pancreatogenic diabetes, namely type 3c diabetes *mellitus* (DM3c) which is characterized by an absent pancreatic polypeptide response to mixed-nutrient ingestion [22]. The American Diabetes Association has also recognized this type of diabetes as a special category classified within diseases of the exocrine pancreas (DM3c) [23]. Risk factors for DM3c in CP include longstanding duration of disease, prior partial pancreatectomy and early onset of calcifications. Patients developing DM3c are likely to have pancreatic exocrine insufficiency. The initial evaluation of CP patients includes fasting glucose and HbA1c. The PancreasFest recommendations for diabetes advocate the annual repetition of these tests [22]. There are no specific guidelines on the treatment for DM3c due to lack of studies evaluating the efficacy and safety of the different available diabetes therapies in this setting. The main endocrine defect in these patients is insulin deficiency but they also carry a greater risk of hypoglycemia is treatment with insulin; nevertheless, in the initial phase of the disease, controlling mild hyperglycemia with oral hypoglycemic agents may be valid. In advanced disease, insulin is the only effective therapy, with dosing and regimen following the general recommendations for type 1 diabetes [22].

Pain management

Pain is the most common symptom of CP and probably the most debilitating and challenging to treat. Most patients necessitate some form of analgesia [24]. Significant worsening of pain or change of the usual characteristics or pattern usually implies a differential diagnosis to confirm that it is only an exacerbation of the disease and not another complication such as biliary lithiasis, pancreatic cancer, peptic ulcer disease or other pathology. Imaging as computed tomography (CT), magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS) are useful to identify complications and exclude other differential diagnosis. After confirming pain for CP, the medical approach should begin with optimization of general measures and enzyme replacement therapy. Subsequently, analgesic therapy should be escalated. Analgesics should be consumed before the meal, since a reduction in postprandial pain results in an increased food intake [11].

A randomized, double-blind, placebo-controlled trial of pregabalin proved a more effective pain relief and higher percentage of improvement in health status) after 3 weeks. The initial dose was 75 mg pregabalin twice daily. After 3 days, the dose increased to 150 mg twice daily, with a further increase to 300 mg twice daily after 1 week and for the rest of the study period. If unacceptable side effects were experienced, a single downward dose titration was allowed, with the patient staying on that final dosage for the remaining study [25].

In a double-blind, randomized study, tramadol and morphine showed a potent analgesic effect in severe CP pain when individually titrated. Tramadol was preferred as it interfered significantly less with gastrointestinal function and was more often rated as an excellent analgesic than morphine [26].

In a randomized, double-blind, placebo-controlled, 2-way crossover study in 24 patients, tetrahydrocannabinol was not efficacious in reducing chronic pain resulting from CP [27].

Non-steroidal anti-inflammatory drugs should be preferentially avoided in the long-term due to their gastrointestinal adverse effects and because patients with alcoholic CP have a higher prevalence of peptic ulcers [28].

Evidence from basic science and human studies indicates that pain processing by the central nervous system is abnormal in CP and resembles that observed in patients with neuropathic pain disorders. Therefore, in clinical practice, strategies used for neuropathic pain are transposed to CP. In this context, combined gabapentin and nortriptyline seems to be more efficacious than either drug given alone for neuropathic pain. Therefore, the use of this combination in patients who show a partial response to either drug given alone is recommended for pain relief [29].

The analgesia should follow the WHO's pain ladder for adults as this 3-step approach of administering the right drug in the right dose at the right time is inexpensive and very effective. When pain occurs, it should be promptly dealt with an oral analgesic in the following order: non-opioids (paracetamol); then, if necessary, mild opioids (tramadol) and finally, if unresponsive, strong opioids such as morphine. Adjuvants (such as nortriptyline) are extremely useful for controlling anxiety and fear associated with pain and can be initiated from the first step. In patients with frequent pain episodes, there should be a regular administration of analgesics to maintain pain freedom instead of an "on demand" strategy [30].

Other therapies

In a randomized placebo-controlled double-blind trial, 147 patients with CP were randomized to placebo or antioxidants (organic selenium, ascorbic acid, carotene, tocopherol and methionine) for 6 months. The antioxidant supplementation proved effective in relieving pain and reducing levels of oxidative stress in patients with CP [31]. Contrariwise, another randomized controlled trial involving 71 patients did not demonstrate improvement in pain nor in quality of life with the use of antioxidants. The benefit of its use is therefore yet unclear. The differences in studies might be attributed to different antioxidant composition, study population, pancreatitis etiology, alcoholic and smoking status [32].

After establishing a secure diagnosis, CP requires several focus of treatment. The pain management of CP cannot be left exclusively to a specialist pain clinic, as it is rather distinct from the pain of pancreatic carcinoma, for example. The gastroenterologist has an essential central role in contextualizing the pain (excluding alternative diagnosis and complications), and managing it with the several available therapeutic measures including nutrition, lifestyle modifications, PERT and analgesics. Likewise, we recommend: alcohol and tobacco abstinence, a normal polyfractionated diet and PERT. Analgesia should start with paracetamol. If unresponsive, tramadol is recommended and/or combination with pregabalin. Nortriptyline is a useful adjuvant and if necessary, analgesia may es-

calate to strong opioids. The low evidence about medium-chain triglycerides and antioxidants does not permit a formal recommendation, but due to the low adverse event profile, these therapies might be considered for a trial after discussion with the patient.

Patients with exocrine insufficiency should start PERT and titrate the dose (with PPI) until symptom resolution and normalization of nutritional status. Serum levels to evaluate include vitamins A, D, E, K and B12 levels and secondarily calcium, magnesium, zinc, thiamine and folic acid. All patients should undergo an annual fasting glucose and HbA1c and be treated accordingly if endocrine insufficiency is diagnosed.

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4.2. Endoscopic treatment

Rodrigo Liberal and Eduardo Rodrigues-Pinto

Clinical management of chronic pancreatitis (CP) is often challenging. Between 30 to 60% of patients with CP will ultimately require some type of endoscopic or surgical intervention for treatment. There is a variety of endoscopic techniques that have been used with variable success in the treatment of symptoms or adverse events (AEs) associated with CP. These techniques are often used in combination with medical therapy and attempted before major operative interventions are pursued. However, regardless of the modality, they are often ineffective unless smoking and alcohol cessation is not achieved [1].

The indication for endoscopic therapy is most often intractable pain and treatment should be considered before patients become opiate-dependent. The most common indications for endoscopic treatment are strictures of the pancreatic duct, obstruction of the common bile duct and pancreatic pseudocysts [2]. Endoscopic therapy should be considered as the first-line therapy for painful uncomplicated CP. Clinical response should be evaluated at 6-8 weeks; if it appears unsatisfactory, the patient's case should be re-evaluated and surgical options should be considered, in particular in patients with a predicted poor outcome following endoscopic therapy [3].

Pancreatic duct decompression

Pancreatic endotherapy may be effective in relieving pain in individuals with uncomplicated chronic calcific pancreatitis and should be considered as the first-line therapy for ductal decompression [1]. Endoscopic retrograde cholangiopancreatography (ERCP) can achieve main pancreatic duct (MPD) drainage by sphincterotomy of the major and/or minor papilla, short-term stent placement or pancreatic stone extraction, usually after fragmentation with extracorporeal shock wave lithotripsy (ESWL). The best candidates for successful treatment of painful CP are patients with distal obstruction of the MPD (single stone and/or single stricture in the head of the pancreas) and in the early stage of the disease [4]. In a large multicenter study of endoscopic therapy in CP, MPD obstruction was caused by strictures (47%), stones (18%) or a combination of both (32%); drainage of pseudocysts and treatment of common bile duct strictures were performed in 17% and 23% of patients, respectively [5].

PANCREATIC DUCT STONES

Pancreatic duct (PD) stones are a common complication of CP and produce pain by causing upstream dilation and ductal hypertension. They are seen in approximately 50% of patients with CP. Different classifications of PD stones have been proposed, based on radiopacity or location. Ductal decompression can be achieved endoscopically in several ways. Stones smaller than 5 mm without any evidence of MPD stricture can typically be removed by a Dormia basket or an extraction balloon after pancreatic sphincterotomy. Complete or partial pain relief after pancreatic sphincterotomy and mechanical stone extraction is seen in 50 to 77%. Although effective, these methods have some limitations [6, 7], proving to be ineffective in cases of stones greater than 5 mm in diameter, located upstream of the MPD stricture or impacted in the head of the pancreas, in which case adjunctive therapies or devices to fragment the stones may be needed. The European Society of Gastrointestinal Endoscopy (ESGE) recommends ESWL as a first step, followed sometimes by endoscopic extraction of stone fragments in the presence of large (>5 mm) obstructive stone(s) located in the pancreatic head, and with ductal stenting in the presence of a dominant MPD stricture that induces a markedly dilated duct [3, 4]. One study comparing the efficacy of ESWL alone versus ESWL followed by stones extraction showed a similar symptomatic control in both groups, with much lower costs when ESWL was performed alone [8]. ESWL should be considered for patients with recurrent attacks of pancreatic pain, moderate to marked changes in the pancreatic ductal system and obstructing ductal stones. Factors associated with long-term pain relief are short disease duration, low frequency of pain attacks before treatment, complete ductal stone clearance, absence of MPD stricture and discontinuation of alcohol and tobacco [4].

Early studies have shown that stone removal from the MPD leads to symptomatic improvement in a considerable proportion of CP patients [6, 9]. However, the quality of evidence of reported results remains low in most of these retrospective observational non-randomized studies. Only two randomized controlled trials compared endoscopic therapy and surgery, and both favored surgery. There were, however, several shortcomings, like low technical success rate and suboptimal procedures compared with previ-

ous studies. Endoscopic therapy should be an option since it is less invasive, being possible in patients with risk factors such as older age and co-morbidities, and may reduce or delay the need for surgery, in which case it can also predict the response to surgical therapy. If clinical success can be obtained with ≤5 endoscopic interventions, the patient will probably achieve long-term favorable outcome [4].

PANCREATIC DUCT STRICTURES

MPD strictures are identified in many patients with CP [5]. Although in most cases they are benign, malignancy should be carefully excluded. Akin to PD stones, strictures cause pancreatic duct hypertension, thus contributing to patients' symptoms. The aim of therapy is to decompress the ductal system by alleviating the narrowed segments.

The most commonly used approach involves pancreatic sphincterotomy, followed by dilation of the stricture, and placement of a pancreatic duct stent. This sequence is technically successful in the majority of cases [10]. The stent size should be at least as large as the PD, in order to dilate the stenosis. The 10 Fr is less likely to be obstructed, although its placement is more difficult than a 5 Fr stent. The stents should be long enough to overpass the stenosis, and short enough to minimize the ductal changes.

A prospective study reported rapid symptomatic improvement following insertion of a pancreatic stent in non-operable patients, although further interventions were frequently needed [11]. Removal of the obstruction of the PD is effective for the treatment of pain in the short term, with reported success rates ranging from 37 to 94%. A large study, including over 1000 patients, reported long-term pain relief in 84% of patients [5]. The same study showed that 79% and 97% of patients required new stent therapy for pain control within one and two years after the first procedure respectively. In a randomized study, which included 41 consecutive CP patients with a dominant stricture, showed that pain recurred in 15% of patients with PD stenting versus 50% of control patients over a follow-up period of 62.5 months [12].

There is no consensus for how long stent therapy should be pursued, though some studies suggested that placement of a stent every 6 months achieves symptomatic control in the majority of patients. It should be noted that PD stenting is associated with AEs such as stent occlusion and stent migration (both distal to the duodenum and proximal into the PD). The ESGE recommends treating dominant MPD strictures by inserting a single 10 Fr plastic stent, with stent exchange planned within 1 year even in asymptomatic patients to prevent AEs related to longstanding pancreatic stent occlusion [3]. Simultaneous placement of multiple, side-by-side, pancreatic stents could be applied more extensively, particularly in patients with MPD strictures persisting after 12 months of single plastic stenting. Even though preliminary studies suggest temporary placement of fully covered self-expanding metal stent (FCSEMS) is safe and allows resolution of MPD strictures plus pain relief in a majority of patients, it should only be performed in the setting of trials [3].

Pancreatic pseudocysts drainage

Pseudocysts develop in 20% to 40% of patients with CP. Intraductal hypertension within the MPD or the rupture of a branching duct can lead to its formation. Drainage is indicated in pseudocysts that do not resolve spontaneously and are symptomatic, in particular if there is pain, infection or evidence of obstruction of patients with CP [13, 14].

Pseudocyst drainage can be done percutaneously, endoscopically or surgically. Compared with surgery, endoscopic drainage of uncomplicated pseudocysts provides similar long-term results at a lower cost, with shorter hospital stay, better quality of life during the first months following treatment and a slightly lower procedure-related mortality.

When drainage is indicated, and before selecting the endoscopic approach, it is essential to accurately determine whether there is communication with the main or secondary PDs [15]. There are two different endoscopic strategies for managing pseudocysts. Transpapillary drainage involves directly inserting a stent through the PD into the collection, or trying to bridge the defect with a stent to prevent further leakage and redirect the flow of pancreatic juices back into the bowel. Transmural drainage consists on placement of double pigtail or self-expanding, lumen-apposing metal stents (LAMS) from the stomach or the duodenum into the cyst cavity. Cystoduodenostomy should be preferred over cystogastrostomy if both routes are deemed equally feasible [2]. At least two double-pigtail plastic stents should be placed and should not be retrieved before cyst resolution as determined by cross-sectional imaging and not before at least 2 months of stenting [3]. Whether drainage by plastic or LAMS leads to a better outcome or to fewer AEs it is still being debated [2]. Depending on the location, combined trans-sphincter, transmural or transab-

dominal ultrasound and CT-guided or laparoscopic procedures may be necessary. Both approaches offer high rates of clinical success [16]. However, it should be pointed out that the technical success of transpapillary drainage is lower compared to the transmural approach. It should be reserved for small (<5 cm) communicating pseudocysts associated with a partial PD disruption [17], since this approach may be associated with lower rates of bleeding and perforation at the same time it allows for detection of PD strictures and stones. However, the transpapillary approach may be burdened by the risks of acute pancreatitis, PD scarring or superinfection of the pseudocyst.

Celiac plexus block

The aim of celiac plexus block is to disrupt the transmission of afferent pain signals from the pancreas. It typically involves the injection of the celiac plexus with a local anesthetic mixed with a corticosteroid. Celiac plexus block is performed via a gastric approach using EUS-guidance and has high success rates and relatively low complication rates. EUS-guided approach is preferred over CT-guided approach since the former is associated with fewer side effects [18]. A prospective randomized study, comparing EUS versus CT-guided celiac plexus block, reported pain relief in some 50% of patients in the EUS group, a percentage that was higher than that achieved when the procedure was performed under CT guidance [18, 19].

Several retrospective and prospective studies put the success rate as high as 95%. However, and despite high rates of technical success, the efficacy in terms of long term pain relief is disappointing. While short-term pain improvement is achieved in nearly half of patients, pain improvement 24 weeks after the procedure was reported in only 10% of patients. Given the low long-term success rates, EUS-guided celiac plexus block should be considered as a temporary measure. For these reasons, the ESGE recommends considering celiac plexus block only as a second-line therapy in patients with limited options; EUS-guided approach should be preferred over percutaneous approach [3].

Benign biliary strictures

Benign biliary strictures are frequent in patients with CP, with an estimated prevalence of 3-46% [20]. Biliary strictures in the context of CP usually correspond to a circumferential fibrocalcific narrowing developing within the pancreatic portion of the common bile duct. In some cases, however, biliary obstruction develops from extrinsic compression related to pancreatic edema or fluid collections. Patients with biliary strictures may present with cholestasis, although many experience several symptoms (pain, nausea, weight loss, jaundice and pruritus), and some may develop cholangitis and biliary cirrhosis.

Indications for endoscopic intervention include, in addition to the presence of symptoms, the development of secondary biliary cirrhosis, common bile duct stones, progression of the biliary stricture based on increased proximal biliary ductal dilation, and persistent (>1 month) jaundice, or alkaline phosphatase (2–3 times the upper limit of normal) [3].

When indicated, the endoscopic management usually involves biliary stenting by ERCP. Balloon dilation alone is rarely performed, since strictures in this setting do not resolve easily. Restenosis with clinical relapse is not uncommon after stent removal [21]. For this reason, it is recommended the placement of temporary (1-year) multiple, side-by-side, plastic biliary stents. An alternative approach is the placement of SEMS. Like stents in the PD, stents in the bile duct need to be regularly exchanged to prevent occlusion and cholangitis. A suggested exchange interval for plastic stents is 3 months, whereas FCSEMS remain open for 6 months or longer [2]. The rate of stricture resolution with plastic biliary stent placement is around 37% over 32 months, while SEMS patency is reported to range from 37 to 100% over a mean follow-up of 45 months [22]. A systematic review comparing the two approaches, showed that clinical success was greater with SEMS (80%) compared with single plastic stents (36%) [23]. However, other studies have shown very high success rates with multiple plastic stents [24], and therefore, current guidelines favor this as the initial approach and does not yet support the routine use of biliary SEMS for this indication [3]. However, FCSEMS seem to improve outcome in case series, non-randomized and randomized trials, with a stricture resolution rate of 76–93% and a recurrence rate of strictures of only 14–15% [2].

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4.3. Surgical treatment

Tiago Bouça Machado and José Costa Maia

Surgical strategy in chronic pancreatitis – the Tower of Babel

In spite of being extensively studied, the etiology of chronic pancreatitis (CP) remains not fully understood, with Opie's theory, described in 1901 [1] and pointing to the increased pressure within the pancreatic duct, being still accepted: high-pressure in the pancreatic duct causes an inflammatory response resulting in fibrosis, which, in turn, will cause loss of the ability to distend when secreting the pancreatic fluid. This process results in pain, the most common symptom in CP, whose mechanism, nevertheless, seems multifactorial with obstruction, inflammation and nervous system involved in its genesis [2-4]. The correlation between the solving of pancreatic ductal obstruction and relief of pain is, however, poor [5], and the rate of progression from early to late stage CP varies from years to decades, with only a subset of patients developing constant pain [6]. According to the North American Pancreatitis Study 2, in patients with imaging diagnosis of CP, only about 40% complained of constant pain [7].

The pancreas was one of the last organs surgeons have approached due to its unfavorable position in the abdomen [8]. There is a saying among surgeons that states "God put the pancreas in the back so that the surgeons won't touch it". Despite that, Walther Kausch performed the first pancreatoduodenectomy (PDD) in 1912, but the "concept" of PDD was always attributed to the work of Allan O. Whipple in the late 1930s. For the most part of the 20th century, pancreatic resection surgery was associated with prohibitive morbidity and mortality, leading some authors to condemn this procedure as recently as in the 1970s [9]. At the beginning of the 1990s, with the advent of specialized centers in pancreatic surgery and large caseloads, there was a huge improvement in surgical outcomes, especially in perioperative morbidity and mortality, including two series with more than 100 cases without mortality [10, 11].

The history of surgery for CP didn't run in the same lane of pancreatic resection surgery. Since resection results were so discouraging, surgeons pursued a different path in CP surgery, preferring drainage to resection. The first drainage procedure for CP is at-

tributed to Link [12] in 1911, who reported the establishment of an external pancreatic fistula in management of this disease. He mobilized the tail of the pancreas, brought it to the anterior abdominal wall and established an external pancreatic fistula. There was a transient pain relief until the closure of the fistula. In 1954, Zollinger presented a pancreato-jejunostomy drainage procedure that involved a pancreatic tail and splenic resection and an end-to-side anastomosis between the distal pancreas and the jejunum [13]. In the same year, DuVal published a very similar operation using an end-to-end anastomosis with a defunctionalized Roux-en-Y jejunal limb [14]. One of the most sounding names in CP surgery is Puestow due to his description of the technique of a longitudinal pancreato-jejunostomy published in 1958 [15]. It consisted in a pancreatic tail and splenic resection with the longitudinal opening of the entire pancreatic duct and the establishment of a latero-lateral pancreato-jejunostomy. In 1960 Partington and Rochelle published a simplified version of the Puestow procedure with the assumption that no pancreatic or splenic resection was necessary, resulting in sparing of endocrine and exocrine function [16]. In this paper, describing seven cases submitted to this procedure, the most striking observation was the immediate relief of pain. In 1972, Beger developed the duodenal preserving pancreatic head resection (DPPHR), assuming the core of CP was located in the head of the pancreas [17]. He devised a partial resection of the pancreatic head, preserving the duodenum and common bile duct, anastomosing a jejunal loop to the remaining pancreas. With this procedure, Beger reported freedom of abdominal symptoms in 91% of patients with 14 years of follow-up, and a mortality of 1.8% [18, 19]. The Beger procedure, however, missed to deal with a potential ductal obstruction, since strictures in the duct are not addressed. For this reason, in 1994 Frey developed a DPPHR procedure that involves excision of the pancreas overlaying the ducts of Wirsung, Santorini and the duct to the uncinate process and opening the main duct in the body and tail of the pancreas. The pancreas is drained to a Roux-en-Y loop of jejunum. One advantage over the Beger procedure is the avoidance of the hazardous transection of the pancreatic neck over the mesenteric vein [20].

In 2001, Büchler published the Berne technique that modifies and combines both Beger and Frey procedures. It involves a wider resection of the pancreatic head than the Frey procedure, but without transecting the neck of the pancreas as proposed by Beger. The head of the pancreas is excised keeping only a thin layer of pancreas in the back and opening the common bile and Wirsung ducts. To establish the continuity, a jejunum loop is anastomosed to the pancreatic "cavity", including the common bile and Wirsung ducts [21].

With the improvement in the outcomes of PDD, this procedure became an option in the management of CP, in addition to the drainage and mixed drainage-resectional procedures previously described. According to Büchler ***et al***., PDD grants a lasting pain relief in about 80% of patients, and is the procedure of choice, in case of suspected malignancy in the pancreatic head [22].

In some patients presenting with pan-glandular inflammation, a total pancreatectomy (TP) may be offered, but resulting in difficult to control, insulin-dependent diabetes. To overcome this, in 1977, Najarian ***et al***. reported the first islet cell auto-transplant (IAT) after TP, with improvement in diabetes control [23]. This procedure involves a TP and, after resection, the islet cells are isolated and infused through the portal vein.

In this setting, the goals of TP are to treat continuous pain, increase quality of life and prevent pancreatic cancer [24]. It was considered a last resort procedure, but with the IAT some authors defend that this option has become more attractive for patients in earlier stages of their disease [25, 26].

With the improvement of endoscopic techniques, CP is a three-player game with medication, endoscopic therapy and surgery as players and the role of each player remains the million-dollar question.

Two prospective randomized trials comparing endoscopic and surgical treatment of CP show an advantage of surgical treatment in the long term pain management, with almost half of the patients submitted to endoscopic procedures undergoing a subsequent surgical procedure [27, 28].

Some harmony may be found in the statement that surgery is the best long-term option for pain management in CP, but there is still no consensus about the best procedure. All previously described surgical procedures, more than showing an evolution and improvement, demonstrate that there is no right answer about what is the best procedure to treat CP.

Drainage procedures like Partington and Rochelle pancreato-jejunostomy are a very safe option in patients with substantially dilated pancreatic duct (>7 mm) but this only occurs in less than a quarter of patients [22]. Furthermore, this approach has proven insufficient to deal with pain when the pancreatic head is not adequately drained [29].

When CP is associated with inflammatory mass of the head of the pancreas, pancreatic head resection, associated or not to a drainage procedure, is the technique of choice [30]. The supporters of DPPHR, argue that this procedure improves endocrine and exocrine functions and results in better postoperative quality of life, when compared to PDD [31, 32]. It is not easy to say which DPPHR procedure is the best. The Berne technique is easier to perform than the Beger procedure, but there are no significant differences between them in relevant patient outcomes [8].

There is a consensus that PDD and distal pancreatic resections should be the treatment of choice in cases when malignancy is suspected [30]. The incidence of pancreatic cancer is increased in CP [33] with, at least, a risk 3-fold higher than in the general population. According to Beger ***et al.***, 6% of patients with an inflammatory mass in the head of the pancreas developed pancreatic cancer over a 9-year period [17]. Once CP features are present, the ability to differentiate between inflammation and pancreatic cancer is limited with current imaging or endoscopic ultrasound. When a suspicious pancreatic mass is present, even in the absence of pathologic confirmation, resection should be performed [30].

A prospective trial comparing PDD with DPPHR concluded that patients submitted to DPPHR have better quality of life scores [34]. Belina ***et al***. comparing PDD to DPPHR, also concluded that although both procedures significantly improve the quality of life, the improvement was more significant in DPPHR [35]. Strate ***et al***., comparing long-term results of PDD versus DPPHR (Frey procedure), concluded that there were no significant differences in terms of quality of life, pain control or other somatic parameters with a median follow-up of 7 years [36]. Because CP surgical caseload is small, a good argument in favor of PDD is that it is a much more frequently performed operation that a hepato-pancreato-biliary surgeon is more comfortable performing, than a very specific CP pancreatic surgery like a DPPHR procedure.

Especially in North America, enthusiasts of total pancreatectomy with islet cell auto-transplant (TP-IAT) suggest that it has a definite role in the treatment of CP, particularly in cases in which patients present with parenchymal calcifications involving the whole organ with non-dilated main pancreatic duct, or in patients with refractory pain who have failed to respond to previous endoscopic and surgical treatment [37]. In the same direction, the PancreasFest recommendations for TP-IAT include intractable pain in whom medical, endoscopic or prior surgery have failed, but do not specify the timing to propose surgery, only stating that patient and disease characteristics should be considered [6].

In spite of the number of studies and publications, including several international guidelines, there is no agreement about the timing of surgical treatment in CP. It is hard to determine the correct timing for surgery, but evidence is mounting that timely surgical intervention can at least delay the progression of pancreatic insufficiency [30, 35]. In an international survey, 58% of the pancreatic specialists regard early surgical intervention (as soon as opioid analgesics are required) as being superior to the step-up approach of medical treatment, followed by endoscopic interventions and surgery as a last resort [37]. Ahmed Ali ***et al***. states that surgery should be considered earlier in the course of CP, suggesting that it should be proposed within 3 years of symptom evolution [38]. In the same sense Yang ***et al***. suggest that surgery within 26.5 months of diagnosis is associated with improved pain control results [38]. Several studies show that surgery in the later stages of CP results in central sensitization [40, 41], poor pain relief [39] and increased risk of cancer [42]. In order to answer to this question, the Dutch Pancreatitis Study Group enrolled a trial (ESCAPE) to determine if early surgery is more effective that late stage surgery, but no results are yet available [43].

In the majority of our CP patients, the main etiologic factor is alcohol consumption and so there is some degree of reluctance in offering a complex surgery to a patient that bears an addiction with very high social, psychological and physical burdens. Looking back into the past provides a perspective into the complexity of these patients, since in the 1950s Partington and Rochelle performed their drainage procedure in 6 out of 7 patients that "were severe alcoholics, three having ***delirium tremens*** while in the hospital" [16]. One of the selection criteria for any operative procedure is, therefore, the commitment of the patient to alcoholic abstinence and to actively enroll in rehab programs.

In conclusion, surgery retains a major role in the treatment of CP patients with chronic pain or suspected pancreatic mass. Other complications like biliary obstruction, gastro-duodenal obstruction, pseudocyst and gastrointestinal hemorrhage should be dealt with by endoscopic techniques, reserving surgery for the cases of therapeutic failure. Like in the Tower of Babel tale, there are a lot of players, information and technical advances but a lack of consensus. Timing and the best surgical procedure are not yet clearly

defined, underlying the idea that individual patients with this complex disease should be discussed and treated by experienced teams of gastroenterologists, radiologists, surgeons and nutritionists in a multidisciplinary environment.

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