Italian Journal of Medicine (2012) 6, 236—241

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UPDATES GUIDELINES

Chronic pancreatitis: from guidelines to clinical practice

Pancreatite cronica: dalle linee guida alla pratica clinica

Generoso Uomo [a,*], **Maurizio Ventrucci** [b]

[a] *Internal Medicine Unit 3, Cardarelli Hospital, Napoli, Italy*
[b] *Internal Medicine Unit, Bentivoglio Hospital, Bologna, Italy*

Received 8 July 2011; accepted 11 October 2011
available online 28 January 2012

KEYWORDS
Chronic pancreatitis;
Guidelines;
Pancreatic exocrine insufficiency;
Pancreatic diabetes;
Diagnosis;
Abdominal imaging;
Treatment.

Summary
Introduction: The paucity of specific standardized criteria leads to uncertainties in clinical practice regarding the management of chronic pancreatitis (CP).
Objectives: This paper reports some of the systematic guidelines for the diagnosis and treatment of CP recently elaborated by an Italian multicenter study group. We review recommendations on clinical and nutritional aspects of the disease, assessment of pancreatic function, treatment of exocrine pancreatic failure and secondary diabetes, treatment of pain, and prevention of painful relapses. The review also looks at the role of endoscopy in the management of pancreatic pain, pancreatic stones, duct narrowing and dilation, and complications; the appropriate use of various imaging techniques, including endoscopic ultrasound; and the indications for and techniques used in surgical management of CP.

Introduction

Chronic pancreatitis (CP) is a progressive inflammatory disease in which pancreatic secretory cells are destroyed and replaced by fibrous tissue [1—3]. Abdominal pain is the main symptom in the early phase of the disease; in the long run, malnutrition due to exocrine insufficiency and diabetes appear. For these reasons, patients affected by CP are frequently observed in Internal Medicine wards and Internists should familiarize with the disease. Over the last years many international studies concerning diagnosis and treatment of CP appear in English literature but, only recently, the first official guidelines on CP have been published by an Italian multidisciplinary group of experts under the sponsorship of the *Italian Association of Study of Pancreas* [4].

* Corresponding author: Internal Medicine Department, Unit 3, Cardarelli Hospital, via Cardarelli 9 - 80131 Napoli, Italy.
E-mail: g.uomo@aocardarelli.it, gene.uomo@gmail.com (G. Uomo).

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doi:10.1016/j.itjm.2011.10.004

The present article reports some of the topics of these guidelines with the aim to furnish useful information for physicians facing up the diagnostic and therapeutic challenges of CP in the daily clinical practice.

Structuring of the Italian guidelines for chronic pancreatitis

The primary target of the Italian guidelines was to provide clinical guidelines for appropriate management of CP. Particular forms of CP (autoimmune pancreatitis, paraduodenal pancreatitis and pancreatitis associated with gene mutations) were preliminarily excluded because available data were considered insufficient for generating specific guidelines so far [5,6]. The scientific board selected five main areas of interest in CP: clinics, medical therapy, diagnosis and imaging, endoscopy, and surgery. Relevant questions for each specific area of interest were formulated. The format of recommendations was comprehensive of the question, the statement (53 statements were finally presented), its level of evidence (EL) and strength of recommendation (RG). In addition, statements were accompanied by qualifying comments, written by each working party and reviewed by the scientific board, by taking into account relevant comments and suggestions of the global consensus group too.

Selected topics of the Italian guidelines for chronic pancreatitis

We have selected 31 out the 53 questions reported in the Italian guidelines for CP; statements represent the answers and are accompanied in many cases by specific comments. In addition, we have shortened some comments, trying to give the most practical information.

Clinical, functional aspects, and medical therapy

This section concerns the clinical aspects, exocrine function and medical therapy of the disease. Long-term outcome, pain, pancreatic failure, diabetes and risk of cancer were considered. Main references are [7—15].

Question: Are there different patterns of pain in CP?
Statement: Episodic or persistent types of pain can be present in the clinical picture of CP (EL 2b — RG B).
Comment: Abdominal pain is the dominant symptom of CP. Throughout the course of the disease, 80-90% of patients complain of pain, whereas the remaining 10 to 20% of individuals have ''painless pancreatitis''. Pain is usually recurrent and it may be either episodic (type A: short-lived bouts of pain, lasting less than 10 days with long pain-free intervals; more frequent in idiopathic senile or late onset CP) or persistent (type B: more severe and long-lasting episodes separated by 1-2 month pain-free intervals, more frequent in alcoholic CP and idiopathic juvenile or early onset CP).

Question: Does smoking withdrawal reduce pain relapses in CP?
Statement: Smoking withdrawal is moderately effective in reducing pain relapses in CP (EL 4 — RG C).
Comment: It is difficult to distinguish the role of smoking from that of alcohol consumption in causation and clinical evolution of CP, as cigarette smoking is often an inseparable habit in alcoholics. Moreover, alcohol withdrawal is quite often not associated with smoking withdrawal. Retrospective data indicate a beneficial effect of smoking withdrawal to reduce/avoid pain and complications in CP.

Question: Is alcohol withdrawal recommended for reducing pain in CP?
Statement: Alcohol withdrawal is recommended for reducing pain in CP (EL 2b — RG B).
Comment: Abstinence from alcohol is an important factor influencing pain in patients with alcoholic pancreatitis. Abstainers have a slower rate of deterioration of pancreatic function and a better response to pain control by therapy than non-abstainers. Moreover, exocrine pancreatic insufficiency does not progress after alcohol withdrawal.

Question: Is chronic pancreatitis a risk factor for pancreatic cancer?
Statement: Incidence of pancreatic cancer is increased in long-lasting CP(EL 1b — RG B).
Comment: The relation of CP to pancreatic cancer has been addressed in several epidemiologic case-control and cohort studies. In the only one study in whom the chronic type of pancreatitis was clearly stated and having an high number of patients a clear relationship between CP and pancreatic cancer was found. Cohort studies confirmed the relationship between CP and pancreatic cancer.

Question: Is pancreatic function testing useful for the diagnosis of CP?
Statement: Pancreatic function testing may be used for the diagnosis of CP when imaging is not conclusive (EL 1c — RG B).
Comment: To detect mild or moderate exocrine pancreatic impairment, invasive tests employing a hormonal secretagogue, maximally stimulating pancreatic secretion can be useful. Such tests are sensitive but poorly specific, i.e. they are not diagnostic per se. Conversely, tubeless tests of pancreatic function (faecal elastase, faecal chymotrypsin) can detect only severe exocrine insufficiency.The faecal elastase-1 test does not require a timed stool collection or a special diet, possesses a high negative predictive value for pancreatic insufficiency and has good sensitivity in patients with moderate and severe pancreatic failure.

Question: Is the assessment of endocrine pancreatic function recommended in CP?
Statement: Assessment of endocrine pancreatic function is recommended by measuring fasting blood glucose levels (EL 4 — RG C).
Comment: As there is a high frequency of diabetes in the long-term evolution of CP, it is recommended that fasting blood glucose levels be measured.

Question: Which analgesics are recommended for treating pain in CP?
Statement: Non-steroidal anti-inflammatory drugs (NSAIDs) and narcotics are recommended for treating pain in chronic pancreatic (EL 4 — RG C).

Comment: Conventional NSAIDs represent the first approach to manage pain in CP, but most patients with relentless pain require narcotics. Tramadol should be initially preferred to morphine because of less interference with gastrointestinal functions. Opioids in different formulations are similarly effective.

Question: Is a change in the diet content of carbohydrates, fats and proteins indicated in CP?
Statement: A reduction in dietary fats is recommended if steatorrhea is severe and not responder to medical treatment (EL 5 — RG D).

Question: Is vitamin supplementation recommended in patients with CP?
Statement: Parenteral injection of lipophylic vitamins is strongly recommended in patients with severe exocrine pancreatic insufficiency (EL 1c — RG B).

Question: Are Medium Chain Triglycerides (MCT) indicated in the diet of patients with pancreatic insufficiency?
Statement: MCT are not indicated in patients with pancreatic insufficiency (EL 1b — RG B).

Question: Is pancreatic enzyme supplementation indicated in CP?
Statement: Pancreatic enzymes are indicated in patients with CP and exocrine pancreatic insufficiency (EL 1a — RG A).
Comment: The main clinical consequence of CP is malnutrition due to fat maldigestion and steatorrhoea. Enzyme supplementation improves fat absorption in patients with CP and pancreatic exocrine insufficiency. Enzyme replacement therapy is able to normalise nutritional parameters such as liposoluble vitamins, prealbumin, and ferritin in patients without overt steatorrhoea. Steatorrhoea occurs late in CP (after a median time of 10 to 12 years from the onset of the disease in about 50% of patients), and it may be much more common than expected on a clinical basis only. Therefore, enzyme supplementation should be considered in patients with long-lasting CP.

Question: Is pancreatic enzyme supplementation recommended for reducing frequency and severity of painful relapses?
Statement: Pancreatic enzymes are not recommended for reducing frequency and severity of painful relapses in CP (EL 1a — RG A).

Question: How can the efficacy of pancreatic enzyme supplementation be assessed?
Statement: The clinical improvement of the nutritional parameters and the normalization of gastrointestinal symptoms are sufficient criteria to evaluate the efficacy of pancreatic enzymes. In not-responder patients laboratory methods to assess fat absorption (Coefficient of Fat Absorption, C14 breath test) may be used (EL 2a — RG B).

Question: Should proton pump inhibitors be associated with pancreatic enzymes in the treatment of pancreatic insufficiency?
Statement: Proton pump inhibitors may be associated if steatorrhoea is not controlled by pancreatic enzymes alone (EL 2a — RG C).

Comment: The concomitant use of Proton Pump Inhibitors (PPIs) and pancreatic enzymes is not indicated in patients with an adequate response to enzyme replacement therapy. However, patients with pancreatic insufficiency can have severely impaired pancreatic bicarbonate secretion which may be insufficient to neutralise the acidity of the chyme in the duodenum. This can impair the enzyme supplementation therapy, even though an adequate or high enzyme dose is given. A combination of PPIs is recommended in refractory steatorrhoea only. There is, however, no clear evidence of a clinical advantage for PPIs associated with enteric-coated-microgranule enzyme preparations.

Question: Which pancreatic enzyme formulation should be used and how should it be administered?
Statement: Pancreatic enzyme formulations with enteric-coated pH-sensitive minimicrospheres and high lipase content should be used (EL 1b — RG A). The recommended dose is 25,000—40,000 units of lipase per meal. Pancreatic enzymes should be administered during or just after meals (EL 2b — RG B).
Comment: The efficacy of pancreatic enzyme preparations depends on the enzyme activity released in the duodenum together with the chyme duodenal load. In pancreatic enzyme supplements, pancreolipase is formulated within pH-sensitive enteric-coated microspheres which mix with the meal in the stomach, protect their enzyme content from gastric acidity and empty into the duodenum with the chyme, where coating rapidly disintegrates at pH $\geq$ 5.5 to release enzymes from the microspheres. Minimicrospheres of 1.0 to 1.2 mm in diameter have been shown to be emptied simultaneously with the meal and are associated with a 25% higher therapeutic efficacy as compared to 1.8 to 2.0 mm microspheres. Dosage should be tailored according to the severity of maldigestion and the fat content of the meal. A dosage of 25,000—40,000 IU of lipase per meal is recommended. The efficacy of enzyme replacement therapy seems to be higher when enzymes are administered during or immediately after meals.

Question: Does pancreatogenic diabetes require pharmacological and nutritional approaches differing from those of type 1 and type 2 diabetes?
Statement: The treatment of pancreatic diabetes does not differ from that of the type 1 and type 2 diabetes (EL 4 — RG C).
Comment: Pancreatogenic diabetes differs from type 1 and type 2 diabetes because of the high risk of hypoglycaemia and the lower frequency of ketoacidosis due to the impaired secretion of glucagon. Complications, such as macro/microangiopathy, nephropathy, neuropathy and retinopathy, are as frequent as in type 1 diabetes. Diet in pancreatogenic diabetes overlaps that of type 1 diabetes, even though particular care should be paid to the correction of malnutrition, vitamin and oligoelement deficiency, and the prevention of hypoglicaemia with fractionated meals. With regard to insulin supply, the reference glycaemic target is that of type 1 diabetes, unless it has to be slightly elevated in cases of severe hypoglycaemia. An educational program should be undertaken in order to avoid the onset of severe hypoglycaemia; it should be focused on alcohol abolition, oriented physical activity, fractionated meals, and pancreatic enzyme adherence. There is no evidence of a role

for oral hypoglycaemic drugs in the treatment of pancreatogenic diabetes. In insulin-treated patients, caution should be paid to avoid hypoglycaemia.

Imaging

The role of diagnostic imaging in depicting the early changes in chronic pancreatitis is analysed.

The role of ultrasound-endoscopy in chronic pancreatitis and in the differential diagnosis with pancreatic cancer is discussed. Main references are [9,16—21].

Question: Is transabdominal ultrasound a useful diagnostic imaging technique to confirm the clinical suspicion of CP?
Statement: Transabdominal ultrasound is useful in confirming the diagnosis of advanced CP (EL 4 — RG C).
Comment: Transabdominal Ultrasound (US) is able to confirm the diagnosis of advanced CP since it identifies the thinning of the pancreatic parenchyma, the irregularity of the pancreatic margins, dilatation of the main pancreatic duct and the side branches, and endoductal calcified calculi. Transabdominal US is not able to depict early CP since it does not recognise parenchymal and ductal changes indicative of the early phase of CP.

Question: What is the imaging technique of choice for diagnosing early CP?
Statement: Magnetic Resonance (MR) imaging with MR cholangiopancreatography (MRCP), before and after secretin administration, and endoscopic ultrasound are the most appropriate imaging techniques for diagnosing parenchymal and ductal changes in early CP (EL 3a — RG B).
Comment: Gadolinium-chelate-enhanced MR imaging and MRCP have nowadays substituted diagnostic endoscopic retrograde cholangiopancreatography (ERCP), because they are non-invasive and able to simultaneously assess ductal and typical changes of early CP. MRCP shows a lower spatial resolution as compared to ERCP; however, the administration of secretin during MRCP is able to overcome this limitation. Furthermore MRCP can be acquired dynamically during intravenous secretin administration in order to non-invasively obtain morphologic and functional information.

Endoscopic ultrasonography has recently shown its ability to diagnose early CP by assessing the morphological and structural changes of the pancreatic parenchyma. The meaning of these pancreatic morphological changes in asymptomatic patients with normal pancreatic laboratory tests is not clear.

Question: Is dynamic MRCP during secretin administration useful in patients with CP?
Statement: Dynamic MRCP during secretin administration is a problem solving technique to identify initial morphological changes of the pancreatic duct system and hydrodynamically significant strictures, and to assess the pancreatic exocrine reserve (EL 3a — RG B).
Comment: In early CP, dynamic MRCP during secretin stimulation is useful in confirming the clinical suspicion of CP and in identifying the causes of recurrent CP, by detecting the initial morphological changes of the pancreatic duct system and, specifically, of the side branches. In advanced CP, dynamic MRCP during secretin stimulation is useful in identifying hydrodynamically significant strictures and for assessing the pancreatic exocrine reserve.

Question: Which is the most appropriate imaging technique for the identification of the site and the topography of pancreatic stones?
Statement: The most appropriate imaging technique to define the site and the topography of pancreatic stones is the computed tomography (EL 3 — RG C).
Comment: Computed tomography without contrast media administration is the diagnostic imaging modality of choice in diagnosing pancreatic calculi typically present in advanced CP (both inside the lumen of the main pancreatic duct and/or side branches). Transabdominal US is also able to diagnose pancreatic calculi, especially when they present a diameter $>$ 5 mm and they are localized in pancreatic head but a negative ultrasound does not exclude the presence of stones. Conventional radiology is able to visualize pancreatic calculi, especially coarse stones, but it cannot distinguish their topography. Endoscopic ultrasound is comparable to computed tomography in depicting site and topography of pancreatic calculi, being able to visualize also very small calculi ($<$ 3 mm). However endoscopic ultrasound is a minimally invasive imaging modality and is used as a problem solving technique.

Question: What is the imaging technique of choice for the assessment of a patient with CP and flare-up of the disease?
Statement: Computed Tomography (CT) is the technique of choice in patients with CP and a flare-up of the disease (EL 4 — RG C).

Question: What is the most reliable procedure in detecting malignancy in patients with CP, when clinically suspected?
Statement: The most reliable diagnostic tool in tissue characterisation is represented by EUS with fine needle aspiration (EL 4 — RG C).

Endoscopic and surgical treatment

Main indications for endoscopic and/or surgical treatment of patients with painful CP and complications are presented. Main references are [12,22—30].

Question: Is endoscopic therapy effective for treating pain associated with main pancreatic duct dilation in CP?
Statement: Endoscopic therapy is effective in patients with pain and main pancreatic duct dilation (EL 3b — RG B).
Comment: Endoscopic treatment is effective in short-term follow-up in patients suffering from obstructive type pain. Despite its short-term efficacy, endoscopic therapy does not affect quality of life. Endoscopic therapy can affect the long-term clinical outcome by decreasing both the hospitalization rate for pain and the intake of analgesic intake. Because of the frequent coexistence of different ductal lesions in the same patient, the effectiveness of the endoscopic therapy is usually the result of combined procedures, such as sphincterotomy, stricture/s dilation, stone/s extraction, stent/s placement. The aim of all these endoscopic procedures is to restore a drainage of main pancreatic duct. In the presence of intraductal obstructing stone(s), endoscopic therapy may be combined with Extracorporeal Shock Waves Lithotripsy (ESWL). Endoscopic drainage can be proposed as a first-line

treatment in patients unfit for surgery or surgery refusing and can be useful also as a ''bridge to surgery'' therapy.

Question: Should ESWL be associated with endoscopic therapy in patients with pain and stones in the main pancreatic duct?
Statement: Endoscopic therapy should be associated with ESWL in presence of large and obstructive stones of the main pancreatic duct (EL 2c — RG B). In patients with stones in the head or in the body of the pancreas, and without strictures of the main pancreatic duct, ESWL alone is equally effective as combined with endoscopic treatment (EL 1b — RG A).
Comment: ESWL is required in 36-68% of patients and successful rate of stone clearance of the main pancreatic duct ranged from 37 to 100%. Use of ultrasound instead of X-rays to locate pancreatic stones is associated with a lower fragmentation rate.

Question: Is endoscopic therapy indicated in patients with CP and cholestasis, jaundice or cholangitis?
Statement: Endoscopic therapy is indicated as a temporary effective treatment of cholestasis, jaundice or cholangitis in patients with CP (EL 4 — RG C).
Comment: Plastic stent placement is effective for short-term resolution of symptomatic biliary strictures. Stent malfunctioning with clogging and septic complications are common. Morphological resolution of stenosis in long-term follow-up studies is obtained in no more than 10% of patients. More aggressive endoscopic therapy, by placement of multiple plastic stents can obtain stricture resolution in 44—90% of cases with a 13—48 months follow-up period after stent removal. As a definite treatment, stenting should be reserved for patients with serious co-morbid disease or who refuse surgery.

Question: Is endoscopic therapy indicated in asymptomatic patients with CP and dilation of the main pancreatic duct?
Statement: There is no indication to endoscopically treat asymptomatic patients with dilation of the main pancreatic duct (EL 5 — RG D).

Question: Is biliary endoscopic drainage indicated in asymptomatic patients with normal liver function tests in the presence of common bile duct stenosis?
Statement: Endoscopic therapy is not indicated in presence of common bile duct stenosis and dilation in asymptomatic patients with normal liver function tests (EL 5 — RG D).

Question: Is endoscopy indicated for the treatment of pancreatic pseudocysts?
Statement: Endoscopic therapy is indicated in symptomatic or complicated non haemorrhagic pancreatic pseudocysts (EL 4 — RG C).
Comment: Most pancreatic pseudocysts are asymptomatic and resolve spontaneously. Treatment of asymptomatic and uncomplicated pseudocysts is not indicated, regardless of the size. Pseudoaneurysms are relatively frequent in association with pancreatic pseudocysts. Haemorrhagic pseudocysts are an absolute contraindication for endoscopic drainage.

Question: Which are the indications for surgery in patients with CP without extrapancreatic complications?
Statement: Disabling and severe pain is the main indication for surgery (EL 4 — RG C); the other indication for surgery is suspicion of pancreatic cancer (EL 4 — RG C).
Comment: Although there is no prospective randomized study comparing conservative and surgical treatment, there is evidence that surgery is effective in pain. Surgery, tailored to the presumptive pain cause, provides lasting pain relief. As concerns suspicion of cancer, three different settings should be considered: 1. the association between CP and pancreatic cancer; 2. the need to distinguish between central intraductal pancreatic mucinous neoplasia and CP to avoid incorrect conservative management; 3. the need to diagnose an autoimmune pancreatitis to avoid unnecessary resections. The improvement in preoperative diagnostic tools (endoscopic US, CT, MRI, PET, histology, laboratory tests) allows the correct diagnosis in most cases of malignancy suspicion. However, if the suspect of cancer can not be ruled-out, the patient should undergo a resective operation and not a derivative one, to obtain adequate material for histological diagnosis. The delay in the treatment of pancreatic cancer due to misdiagnosis is often fatal.

Question: Which are the indications for surgery in patients with extrapancreatic complications of CP?
Statement: Bile duct and duodenal symptomatic obstructions are indications for surgery (EL 4 — RG C); symptomatic pseudocysts can be treated by surgery or endoscopy (EL 4 — RG C); variceal bleeding due to splenic vein thrombosis should be treated by splenectomy (EL 4 — RG C); prophylactic splenectomy may be considered when a patient with asymptomatic gastric varices due to splenic vein thrombosis is undergoing surgery for other complications of CP (EL 5 — RG D).

Question: When is the appropriate timing for surgery in painful CP?
Statement: Pancreatic surgery should be performed after failure of medical treatment and to avoid narcotic addiction, and decided in a meeting of the patient with an experienced surgeon and a gastroenterologist (EL 5 — RG D).
Comment: Studies evaluating the natural course of pain in CP documented a variable percentage of patients (47—80%) achieving spontaneous pain relief in advanced CP (10—15 years from onset). However, remission is unpredictable and a percentage of patients will suffer of pain indefinitely. There is no pain level to define the timing of operation, but a delay in treatment may affect quality of life, increase medical and social costs and cause narcotic addiction.

Conclusions

Relevant messages for the management of CP in daily clinical practice may be summarised as follows.

- Most patients present a typical abdominal pain requiring an adequate treatment.
- Withdrawal of alcohol consumption and smoking is extremely important.
- Faecal elastase assay is the most useful pancreatic function test to confirm exocrine insufficiency, abdominal US and CT scan are useful diagnostic tools in the advanced stage of CP, while MR imaging and endoscopic US represent the best diagnostic methods in the earlier stage.
- Possibility of malignancy development during the course of the disease should be always considered.

- The vast majority of patients requires pancreatic enzyme supplementation in adequate dosage and preparations.
- Clinical manifestations of diabetes due to CP are little bit different from that of the classical form of type-1 and -2 diabetes, even if the treatment is similar.
- Endoscopic therapy with ESWL is a valuable option in symptomatic patients with dilation/stones of the main pancreatic duct.
- Surgery should be indicated for pain unresponsive to other treatments and, most of all, when the suspicion of malignancy is present.

Conflict of interest

The authors have no conflict of interest to declare.

Acknowledgements

The authors acknowledge the President and the Council of the *Italian Association of Study of Pancreas* for the permission to report part of the official recently licensed guidelines for CP and the guest editors of the original article *Italian Consensus Guidelines for CP* (L. Frulloni, G. Delle Fave and I. Vantini). Statements not reported in the present issues and the whole bibliography are available into the original article [4].

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