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REVIEW

Chronic pancreatitis: an overview of diagnosis and management

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ABSTRACT

Introduction: Chronic pancreatitis entails a heavy burden on the healthcare system because of its often protracted evolution, requiring complex diagnostic and therapeutic procedures.

Areas covered: This review focuses on novel imaging and endoscopic diagnostic and therapeutic interventions that have changed the management of patients with chronic pancreatitis. We have conducted an extensive search of original papers and guidelines, in order to provide a comprehensive and up to date review of available evidence in these areas of interest.

Expert opinion: The traditional challenges in managing chronic pancreatitis patients stemmed from the limitations of diagnostic modalities, which could not correctly identify patients in an early stage of the disease, as well as from the scarcity of therapeutic options available. Advances in imaging of CT-scan, MRI, and EUS have opened the way for early diagnosis and staging. This has allowed more aggressive and tailored therapeutic modalities, particularly in endoscopic therapy and minimally invasive surgical interventions. Although high-quality data from large RCTs is still scarce, evidence-based algorithms for diagnosis and therapy are now changing the way we address this chronic disease. In the near future, we can expect a tailored approach based on patient and disease-related predictive factors, relying on a vast armamentarium of endoscopic and surgical solutions.

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Chronic pancreatitis; endoscopic ultrasound; endoscopic retrograde cholangiopancreatography; magnetic resonance imaging; pain management; endoscopic stenting; surgery

1. Introduction

Chronic pancreatitis (CP) is an inflammatory condition associated with progressive fibrosis of the pancreas, causing irreversible parenchymal and ductal changes which, over time, can ultimately lead to exocrine and/or endocrine pancreatic insufficiency [1,2]. Chronic abdominal pain is the most common symptom of CP, with symptoms of exocrine and/or endocrine dysfunction usually appearing late in the course of the disease.

Traditionally, a definitive diagnosis of CP was made in the late stages of the disease, and therapeutic options to treat the symptoms and complications of CP were quite limited. Recent advances in cross-sectional imaging and endoscopic ultrasound [3] have significantly refined the diagnostic workup, while the progress of endoscopic therapy, especially in the field of endoscopic retrograde cholangiopancreatography (ERCP), has opened up a new spectrum of therapeutic options for CP patients.

Our review will focus on the diagnostic and therapeutic advances in chronic pancreatitis in the adult population, with a focus on the endoscopic management of CP, since research in this field has been particularly fruitful in recent years.

2. Diagnosing chronic pancreatitis

The classical diagnostic paradigm, established in the early 1980 s with the adoption of the Cambridge diagnostic criteria [4], required morphologic changes on either endoscopic retrograde pancreatoscopy, abdominal ultrasound and/or CT scan in order to confirm a diagnosis of CP. However, as cross-sectional imaging became widely available, the diagnostic work-up has moved away from ERCP, a highly invasive procedure, into the realm of noninvasive imaging techniques.

Currently, computed tomography (CT) and magnetic resonance imaging (MRI) are the most useful noninvasive imaging modalities for diagnosing CP and a definitive diagnosis of CP can usually be made on the basis of these imaging modalities, which detect typical findings such as calcifications and ductal and parenchymal changes.

However, current guidelines recognize that CT and especially MRI examinations have limited applications in the early stages of disease [5–7]. Secretin-enhanced MRCP, a functional examination that involves the use of secretin as a stimulant of pancreatic secretion, has been shown to enhance the diagnostic accuracy in the setting of non-calcific, early CP (Figure 1(a, b)) [8]. Dynamic MR imaging using secretin stimulation (Figure

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Article highlights

- Diagnostic accuracy in detecting and staging of chronic pancreatitis has been improved mainly by MRI applications such as T1 mapping, elastography, and measurement of extracellular volume.
- Endoscopic ultrasound examination, enhanced by adjunctive modalities such as fine-needle aspiration/biopsy and contrast enhancement is particularly useful in diagnosing CP in an early stage and discriminating between chronic pancreatitis and pancreatic cancer.
- Endoscopic therapy, including various stenting strategies and pancreatoscopy-guided intraductal therapy, has widened the armamentarium of endotherapy for main pancreatic duct strictures and intraductal stones.
- There is increasing evidence to support early surgical treatment in refractory cases, with a particular interest in the application of laparoscopic and robotic interventions to minimize postoperative complications.

2(a,b)) has two main advantages over conventional MRCP – it allows a significant increase in the number of ducts which can be correctly assessed by the radiologist thereby increasing diagnostic accuracy and it also allows a quantitative assessment of pancreatic exocrine function by assessing the flow of pancreatic juice in the duodenum [9]. However, despite significant improvements in characterization of the PD and, especially, the side-branches of the PD, secretin-enhanced MRCP has a relatively high rate of false-negative results in young patients with early CP when applying the Cambridge criteria against an ERCP diagnostic gold standard [10].

Two main limitations of the classical diagnostic paradigm have been repeatedly underlined: firstly, minimal changes in the early phases of the disease might not be detected or correctly interpreted by either ERP or cross-sectional imaging and secondly, there is an inevitable overlap between morphologic changes in the pancreatic ducts and parenchyma stemming from the chronic inflammatory response in CP and those arising from various other causes, such as age-related degeneration. In recognition of these facts, a mechanistic approach to the diagnosis of early CP has been recently proposed by an international consensus [11]. Under this diagnostic paradigm, early CP should not be diagnosed based on imaging techniques but by shift advocating a combination of a suggestive clinical context, the presence of recognized high-risk factors and biomarkers of CP, and the lack of a more likely cause for the clinical presentation.

One alternative way of addressing the limitations of diagnosis based on ductal changes has been the improvement of methods aimed at quantifying fibrotic changes in the pancreas. Recently, the use of intravoxel incoherent motion (IVIM), a technique based on diffusion-weighted imaging (DWI) during MRI, for the simultaneous estimation of tissue perfusion and diffusion has showed promising results, both in differentiating patients with CP from controls as well as in discriminating between patients with early-stage CP and those with more advanced disease [12]. T1 mapping was shown to be a good tool in discriminating between patients with suspected mild

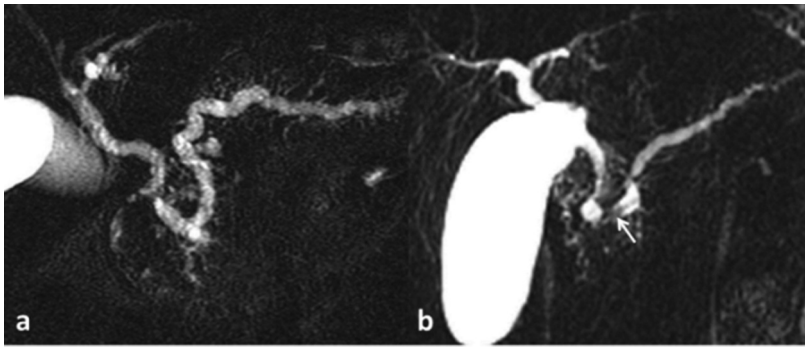

Figure 1. (**a**) RMN image with evidence of dilation of the main pancreatic duct and the secondary pancreatic ducts. (**b**) Chronic pancreatitis with stricture and stone (arrow).

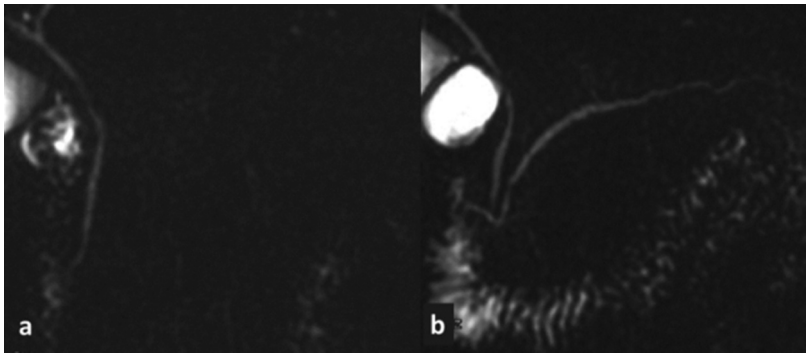

Figure 2. (**a**) RMN in a patient with suspected chronic pancreatitis before Secretin. (**b**) RMN with Secretin is showing pancreas divisum with signs of chronic pancreatitis (initial dilation of secondary ducts on the level of body and tail).

CP and normal controls and increased T1 relaxation times showing good diagnostic accuracy [13].

Extracellular volume fraction (ECV), a marker for tissue fibrosis that has already been adopted in clinical practice for the evaluation of myocardial fibrosis [14], was recently evaluated by the same group of Tirkes et al [15] as a potential tool in diagnosis CP. The study showed a very high diagnostic accuracy for both ECV alone (Area under the receiver operator characteristic – (AUC) = 0.9) and ECV combined with T1 mapping (AUC = 0.94) in discriminating between CP patients and the control group.

One particular challenge for both CT and MRI is differentiating between focal chronic pancreatitis, especially in the head of the pancreas, and pancreatic cancer (PC) [16]. T1 relaxation time, a parameter influenced by the high aqueous protein content in pancreatic acini, seems capable of discriminating between normal parenchyma, mild and moderate/severe CP, respectively [17]. Diffusion-weighed imaging (DWI) MRI remains the most promising modality to help discriminate between these entities, showing high diagnostic accuracy in a recent meta-analysis of available studies; however, the authors agree that additional data is required to validate their initial findings [18].

Finally, another potential application of noninvasive imaging is to discriminate between the stages of CP, which could have prognostic implications for the patients and affect their medical management. MRI elastography, which evaluates the stiffness of pancreatic tissue, showed good diagnostic accuracy in distinguishing between patients with early and moderate/severe CP as assessed at ERCP and a control group [19].

While endoscopic evaluation of the pancreas is a more invasive means of diagnosing CP, it offers some practical advantages over cross-imaging techniques like CT and MRI. Endoscopic ultrasound (EUS) has largely replaced ERCP as the endoscopic method of choice for evaluating suspected CP. The main advantage of EUS over ERCP is the possibility of assessing the parenchymal changes in addition to the ductal changes which constitute the basis of the Cambridge diagnostic criteria in ERCP [20]. EUS findings in CP include calcifications, intraductal stones, hyperechoic foci, stranding, and various ductal changes, which together form the basis of the Rosemont criteria [21] (Table 1). One of the main limitations of EUS diagnosis is the high interobserver variability [22,23]; in addition, according to the Rosemont criteria, pathological findings were grouped into major and minor criteria since they were thought to carry different significances. However, a recent study exploring the relationship between risk factors for CP and presence of major and minor criteria on EUS showed that all findings except the presence of intrapancreatic cysts were correlated with traditional risk factors for CP such as alcohol intake, smoking, and age [24], confirming the validity of the Rosemont diagnostic criteria from a pathology viewpoint. Furthermore, the Rosemont criteria has recently been used as a comparative gold-standard for the development of a novel diagnostic tool using secretin-enhanced MRCP to detect and score CP severity, further confirming the central role of EUS-based diagnostic criteria in the modern landscape [25].

Table 1. Comparison between the EUS-based (Rosemont) and ERCP-based (Cambridge) evaluation in chronic pancreatitis.

	Rosemont criteria (EUS)	Cambridge criteria (ERCP)
Ductal changes	MPD stones (MA) Dilated MPD (>3.5 mm in the body/>1.5 mm in the tail) (m) Irregular duct contour (m) Dilated side branches (>3) (m) Hyperechoic MPD wall (m)	Dilation of MPD Irregularity of MPD Presence of strictures Dilated/abnormal side-branches Presence of cysts
Parenchymal changes	Hyperechoic foci (>2 mm, with shadowing) (MA) Lobularity (≥3 contiguous lobules, 'honeycombing') (MB) Presence of cyst(s) (m) Hyperechoic strands (m) Hyperechoic foci (nonshadowing) Lobularity (noncontiguous lobules)	**Not applicable**
Interpreting imaging findings	**Consistent with**: 2 MA or 1 MA + 1 MB or 1 MA + ≥3 m **Suggestive**: MA + <3 m or MB + ≥3 m or ≥5 m **Indeterminate**: MB + <3 m **Normal**: <3 m	**Normal**: uniform filling of side branches without acinar opacification and normal sidebranches **Equivocal**: normal MPD; 1–3 abnormal branches **Mild**: > 3 abnormal side branches **Moderate**: dilated MPD w/ irregularity; >3 abnormal side branches; Small cysts (<10 mm) **Severe**: large cysts (>10 mm) gross irregularity of MPD; intraductal stones; strictures; obstruction with severe dilation
Comments	Potential bias related to age and gender-related changes in pancreatic morphology[26,27]	Agreement between EUS and ERCP findings is excellent for moderate and severe stages of the disease[28]

MA, major criteria A; MB, major criteria B; m, minor criteria.

EUS also allows for the assessment of tissue stiffness by means of EUS strain elastography [29] and shear-wave measurement (SWM). EUS-SWM seems a very promising diagnostic tool since it is based on an objective measure rather than the operator-dependent findings of the Rosemont criteria. A recent study [30] has shown excellent diagnostic accuracy for EUS SWM in detecting CP as assessed by the traditional Rosemont criteria, thus opening the way for a more objective, operator-independent endoscopic diagnosis of CP.

Finally, EUS is particularly useful in evaluating suspicious pancreatic masses and discriminating between CP and PC, since fine-needle aspiration (FNA) allows tissue acquisition in most cases where diagnosis is unclear. The main problem is that changes of CP limit the accuracy of FNA findings [31,32], making the diagnostic workup of small pancreatic lesions especially problematic in this setting, as recently shown in the study by Kurita et al. [33]. One potential solution would be switching to fine-needle biopsy (FNB) to replace FNA, as the use of biopsy needles provides more tissue with preserved architecture, thereby increasing the diagnostic yield across a variety of indications and irrespective of ancillary factors

such as the presence of an on-site pathologist [34]. Interestingly though, the utility of FNB needles does not seem to extend to beyond confirmation of malignancy; a recent study suggests that diagnostic accuracy for early CP remains suboptimal despite the theoretical advantage of using these large-bore needles while raising safety concerns over tissue acquisition in this setting [35].

Furthermore, adjunctive methods such as contrast-enhanced (CE) examination can significantly increase the diagnostic accuracy of EUS as shown in a recent study by Harmsen et al. [36]. In their patient cohort, high-mechanical index CE-EUS had a 94% accuracy in classifying patients as either PC or CP, which was superior to the performance of multidetector CT scan (83% accuracy) and low-mechanical index CE-EUS, the dynamic EUS method traditionally used in evaluating suspicious pancreatic masses [37,38].

3. Medical therapy

Chronic pancreatitis is the end-stage development of chronic pancreatic damage and no medical therapy has proved effective in reversing its structural changes. Lifestyle measures addressing identifiable risk factors are essential in limiting the damage while medical therapy is geared to the treatment of the main complications of CP: pain, maldigestion, and type 3 c diabetes mellitus.

Treatment of pain is multimodal but should begin with analgesics that are generally adjusted in escalating fashion to control symptoms (the 3-tiered 'pain relief ladder') [39]. The pharmacological algorithm starts with acetaminophen and may lead to tramadol and unconventional adjuvants such as pregabalin, antidepressants, or anticonvulsants and, in later stages, to morphine. Although effective in controlling pain, long-term opioid-based regimens should be avoided, whenever possible, due to the deleterious long-term effects including, among others, constipation, sleep-disordered breathing, fractures as well as the risk of tolerance and overdose. Various antioxidants have also been explored as analgesics but meta-analyses have shown only a slight benefit in this setting. Antioxidant cocktails (L-methionine, β-carotene, vitamin C, vitamin E, and organic selenium), or allopurinol can reduce pain slightly but a strong recommendation cannot be made on the basis of current evidence [40]. A randomized, double-blind, placebo-controlled study showed significant improvement in relevant pain scores that persisted up to 6 months for a combination of antioxidant with pregabalin in a young population of 87 patients with no need for high-potency narcotic [41].

The progressive loss of functional parenchyma leads to secretory insufficiency that affects the exocrine as well as the endocrine component of the pancreas. Even if overt steatorrhea appears only after the secreted lipase level is less than 10% of normal, enzymatic insufficiency may lead to nutritional deficit before this threshold is reached. Therefore, rigorous and repeated nutritional assessment followed by adequate pancreatic enzyme replacement therapy (PERT) is essential in the medical management of patients with CP. According to current guidelines efficient PERT makes use of enteric-coated microspheres or mini-microspheres administered orally with food thus ensuring at least 40,000 units of lipase per main meal [42]. A recent meta-analysis of 17 studies including 511 patients with CP has conclusively shown that PERT significantly improves the coefficient of fat absorption compared to baseline and placebo [43]. Increasing the dosage of PERT or adding gastric acid suppression can improve efficacy in incomplete responders while the uncoated formulation of enzyme supplements may play a role in pain relief. Patients also require regular surveillance of their tolerance to glucose as new onset of diabetes can contribute to malnutrition and needs to be corrected swiftly.

Apart from different formulations of PERT few novel medical therapies have been investigated in recent years. Oral litholysis with long-term trimethadione, an antiepileptic agent that is excreted in pancreatic juice in high concentration presumably dissolving CaCO3, has been reported as efficient in providing chemical dissolution of difficult pancreatic duct stones in a small cohort [44]. Interestingly, these were patients who were not eligible or had failed repeated prior ESWL and endoscopic therapy. Camostat mesylate is an oral serine protease inhibitor commonly used in Japan that is currently undergoing a phase I/II study for CP-associated pain [45]. A phase III, triple-blind randomized placebo-controlled trial comparing simvastatin 40 mg/day to placebo for 1 year in patients with recurrent pancreatitis or acute flares in CP is also currently enrolling with results awaited at the end of 2022 [46].

4. Endoscopic therapy

Endoscopic therapy in chronic pancreatitis is aimed at relieving pain caused by the obstruction of the main pancreatic duct through due to intraductal stones or strictures of the MPD. Although pain is an early symptom, affecting more than 75% of patients with CP at the time of diagnosis [47], there are several underlying pathological mechanisms thought to be responsible for the development of pain in the setting of CP, with neuropathic and dysfunctional pain playing a very important role alongside inflammation in its development of pain. Two main patterns of pain have been defined – intermittent and continuous – and these patterns have been correlated with predicting response to therapy [48].

A stepwise approach to dealing with pain in CP has been advocated, with medical therapy and lifestyle changes recommended as first line, followed by progressively more invasive therapies such as extracorporeal shock wave lithotripsy (ESWL) and endoscopic therapy (Figure 3) and culminating with surgery in patients who do not respond to these modalities. Interestingly, although more than three quarters of patients with CP experience some type of abdominal pain, it has recently been suggested that the need for invasive therapy might be lower than initially expected. Thus, in a recent thorough study from the Olmsted county, spanning almost 30 years, and including data from all the CP identified in this

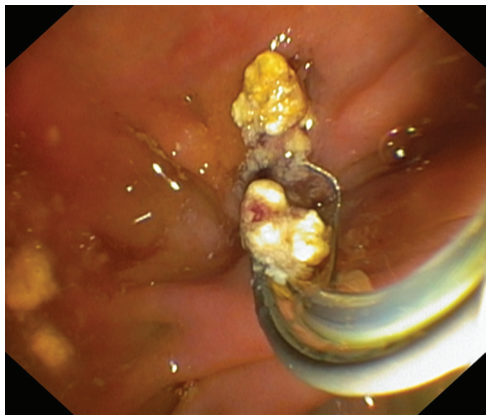

Figure 3. Pancreatic stones are extracted with a Dormia basket after successful fragmentation by Extracorporeal Shock Wave Lithotripsy.

catchment area, the lifelong need for invasive therapy was estimated at 30%, with 23% of identified subjects receiving some form of endotherapy and a further 11% requiring surgical intervention for pain relief [49].

Pancreatic endotherapy addresses two main issues: strictures and stones in the main pancreatic duct (MPD). Recent guidelines from the ESGE recommend that ESWL alone should be attempted to treat radiopaque stones >5 mm located in the MPD, with ERCP reserved for radiolucent stones less than 5 mm or as an adjunctive method when ESWL alone is unsuccessful [50].

Traditionally, stone clearance from the MPD required previous pancreatic sphincterotomy as well as adequate dilation of any strictures downstream from the stone before stone removal was attempted [51]. With this approach, success rates between 50% and 80% were reported across various older studies [51–53]. However, the advent of single-operator cholangiopancreatoscopy, coupled with the possibility for targeted laser or electrohydraulic therapy has opened up the field of pancreatic stone endotherapy (Figure 4) [54]. A recent retrospective multicenter study in patients with previously failed interventions for MPD stones proved that cholangioscopypancreatoscopy with intraductal lithotripsy is both feasible (100% success rate in reaching the MPD stone) and effective (95% technical success) for managing these complex cases where surgery was traditionally considered the only viable alternative [55]. It should be noted, however, that complete stone clearance on the first attempt was only achieved in 68% of the cases, and the authors report a complication rate of 30%, with a 23% rate of postERCP pancreatitis (PEP).

The second endpoint of pancreatic endotherapy, MPD stricture resolution, was modeled after the approach for benign biliary strictures, including those secondary to chronic pancreatitis, where the use of plastic stents (PS) and fully covered self-expandable metal stents (FCSEMS) are the mainstays of therapy [56]. Cremer et al. [57] were the first to report on results of plastic stenting for MPD strictures. Since their pivotal study, patients with MPD strictures were subsequently treated with single PS placed across the stricture, with stent exchange at 6 months' interval and treatment duration of 1 year [50]. This approach is usually successful in most patients with single strictures located in the head of the pancreas, while complex and distal strictures are usually refractory to this therapy [58]. Also pancreatic pseudocyst located in the head/body of the pancreas and communicating with the main pancreatic duct can be successfully drained by transpapillary plastic stenting [50]. Tringali et al. [59] demonstrated pancreatic stricture resolution by multiple plastic stents in 83.3% of the cases after one treatment session, with the success rate increasing to 89.6% after a second treatment session using a mean number of 3 plastic stents (Figure 5). Candidates for multiple stent placement in the MPD should be carefully selected [60] since most patients have no additional benefit from additional stent placement, as shown in another retrospective study of a large cohort of CP patients [61].

Placement of SEMS in the pancreatic duct was first reported by Cremer et al. [62] in 1990. Their initial experience with uncovered SEMS showed good initial results with stricture resolution; however, long-term complications related to the indwelling stents such as ingrowth and stricture recurrence meant this approach was discontinued until the advent of FCSEMS. Theoretically, the removability of these stents encouraged their use in a similar fashion to that employed in treating CP-related strictures of the CBD [63]; however, the recurrence rate in patients treated 8 mm FCSEMS left in the MPD for

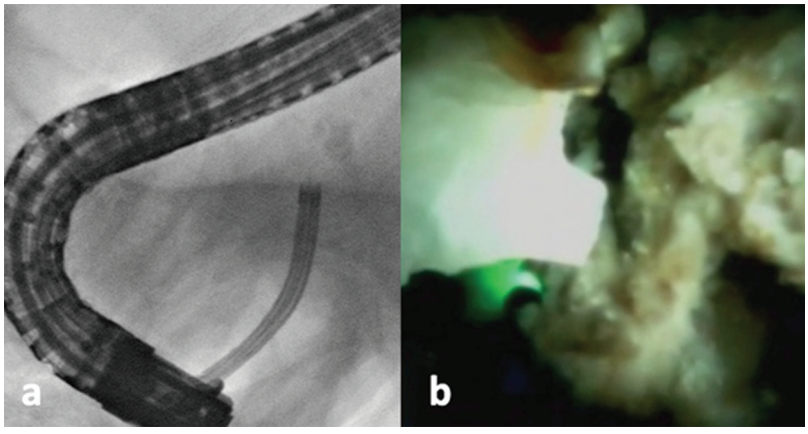

Figure 4. (**a**) Pancreatoscopy with SpyGlass™ DS Direct Visualization System (Boston Scientific Marlborough, Massachusetts, USA) and electrohydraulic lithotripsy of large pancreatic stones; (**b**) Endoscopic view of the stone fragments with the SpyGlass during electrohydraulic lithotripsy.

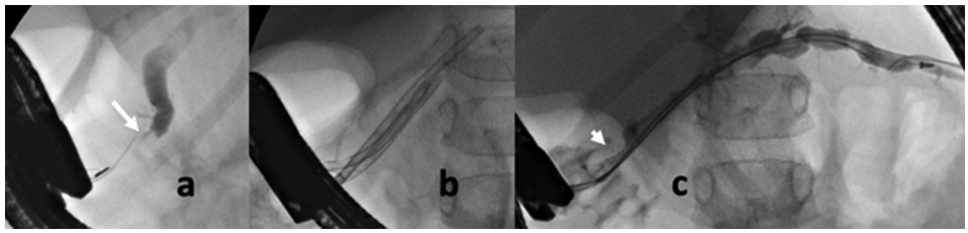

Figure 5. **(a)** Pancreatic duct stricture (arrow) located in the head of the pancreas in a patient with pancreas divisum; three plastic stents are inserted **(b)** and the stricture is resolved (arrowhead) 6 months later after stents removal **(c).**

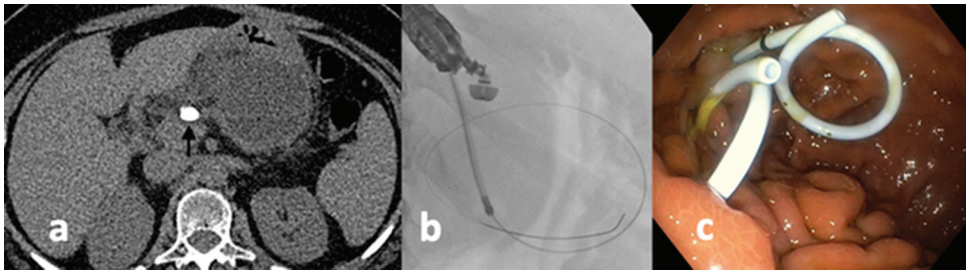

Figure 6. CT-Scan shows a pancreatic pseudocyst above an obstructive pancreatic stone (arrow); (**a**) EUS drainage of the pseudocyst **(b)** by insertion of double pigtails plastic stents **(c).**

3 months was very high (50%) in one of the pilot studies [64]. The significant technical limitations in this area could potentially be overcome by the use of novel, biodegradable stents – either self-expandable [65] or rigid [66] in design. Although such types of stents could, theoretically, offer a 1-stop shop treatment option, by obviating the need for repeat ERCP for stent removal or exchange, clinical success rates remain suboptimal and some authors advocate the need for longer-lasting stent designs in order to ensure adequate and long-term calibration of the MPD [67].

EUS has a key role in CP-related pancreatic pseudocysts drainage especially if larger than 5 cm or located in the tail of the pancreas (Figure 6) [50].

EUS drainage of the PD has been recently proposed as an alternative approach to decompress the MPD in case of ERCP failure, as a means of avoiding surgery [68,69]. Several approaches, via a transgastric or transenteric route are possible, with a high rate of technical and clinical success demonstrated in a recent multicenter cohort study including a large percentage of MPD strictures in the setting of CP (36%) [70]. While traditionally plastic stents were used to drain, the MPD in this setting also SMES with antimigration properties have been used [71–74].

Finally, EUS guided celiac block neurolysis has been advocated for pain control in CP patients [75,76], with a similar approach to that used in PC patients. However, the response rate and overall duration of pain relief are quite underwhelming, with only 55% of patients showing improvement after endoscopic therapy, for a median duration of only 28 days in one recent randomized trial [77].

5. Surgical therapy

Surgical indications for chronic pancreatitis are mainly aimed at pain relief through decompression of the MPD and may include partial resection of the head or body/tail of the pancreas (i.e. Whipple, distal pancreatectomy), drainage procedures (Puestow) and combined partial resection and drainage procedures (i.e. Frey); less frequent indications comprise local complications to adjacent organs and the suspicion of malignancy [78].

Although surgical therapy is usually offered only when conservative and less invasive treatment options fail [79], emerging data suggest that early surgery is associated with reduced risk of pancreatic insufficiency and low re-intervention rates [80] as well as lower use of opioids and better pain relief postoperatively [81]. Current guidelines [62] support the use of drainage procedures (Frey, extended lateral pancreaticojejunostomy on a Roux-en-Y loop) for patients with MPD > 5 mm and normal-size pancreatic head, while advocating for combined drainage and resection procedures in cases of enlarged pancreatic head (Berger and Berne procedures with duodenum-preserving pancreatic head resection).

Taking into account the technical difficulty and potential risks of surgical procedures in the setting of a benign disease, the choice between surgery and endotherapy has been a focus of ongoing debate. Although high-quality evidence from RCT is scarce, a recent Cochrane meta-analysis showed that surgical intervention was superior to endoscopic therapy in terms of pain relief [82]; however, no comparison was possible with regard to procedure-related morbidity and mortality, one of the main concerns for both patient and physician. There is obviously a need for further studies in the field, however, based on available data, current guidelines suggest that early surgery should be proposed within the first 2–3 years after diagnosis, for those patients who had equal to or fewer than five endoscopic procedures, and who have not yet required opioid analgesics for medical pain treatment [75]. While open surgical approach used to be the norm in

older studies, there is a growing body of evidence supporting laparoscopic and even robotic approaches in a variety of clinical scenarios [83–86], which will probably revolutionize the surgical management of these patients, particularly by decreasing the rate of procedure-related complications.

6. Conclusion

In conclusion, the field on minimally invasive diagnosis and therapy for chronic pancreatitis has rapidly expanded over the past decade, with particular advances in the field of MRI and EUS allowing better diagnostic accuracy in detecting CP and characterizing the stage of fibrosis. Furthermore, detection and characterization of pancreatic masses in the setting of chronic pancreatitis, a particularly challenging area, has been facilitated by the advent of DWI MRI, CE-EUS, and tissue acquisition through EUS FNA/FNB.

Endoscopic therapy has also evolved. Although pancreatic endotherapy remains a very demanding technique, with relatively high rates of technical failure and procedure-related complications, several long-term studies confirm the utility of this approach in selected cases. In conjunction with a more aggressive approach to endoscopic therapy, there is increasing evidence to support earlier and more aggressive surgical interventions to ensure better patient-related outcomes.

7. Expert opinion

Although recent advances in both diagnostic and therapeutic interventions for chronic pancreatitis seem very promising, it should be recognized that these applications are usually restricted to expert centers and trial conditions. Furthermore, because CP remains a relatively rare condition, most trials have to rely on small, single-center patient cohorts and many of them have major limitations with regard to study design.

One of the more promising areas of development is the diagnosis and staging of CP severity based on objective measures such as tissue stiffness (ie. EUS-SWM and MR elastography) or fibrosis assessment (ie. MRI ECV quantification), moving away from more operator-dependent evaluations such as the Rosemont and Cambridge criteria. Despite early enthusiasm in this area, we should acknowledge that these remain high-end examinations that still need to prove their applicability in a real-life clinical setting by both confirming the initial results and demonstrating their cost-effectiveness.

However, despite the limitations mentioned above, the increasing availability of EUS and MRI examinations will most likely result in a shift toward an earlier diagnosis in chronic pancreatitis, with many cases diagnosed in a subclinical phase as incidental findings. This provides the opportunity for early therapeutic intervention with lifestyle modification and surveillance, but it could also open the door for over-treatment and an increase in the burden for health-care providers.

Computer-aided diagnosis (CAD), based on machine learning via artificial neural networks, which has recently been successfully applied to colorectal polyp detection and characterization among other applications, could also help with improved lesion detection and characterization in the setting of CP [87], once adequate algorithms are set in place. Although technically more challenging for an application such as EUS, CAD is surely one of the most promising disruptive technologies introduced in the world of endoscopy.

With regard to endoscopic therapy, emerging data support a step-wise approach based on a combination of modalities including ESWL, single and multiple stenting of the PD, and intraductal therapy with either laser or electrohydraulic lithotripsy for selected cases. Faced with an apparent cornucopia of options, the endoscopist will have to tailor each treatment plan according to patient characteristics, preferences, and available local expertise. A multidisciplinary approach, bringing together the radiologist, the endoscopist, the surgeon, and the pathologist, will be essential to ensure the best outcome for the patient, by incorporating all the aforementioned technical innovations. As such, we believe these patients should be

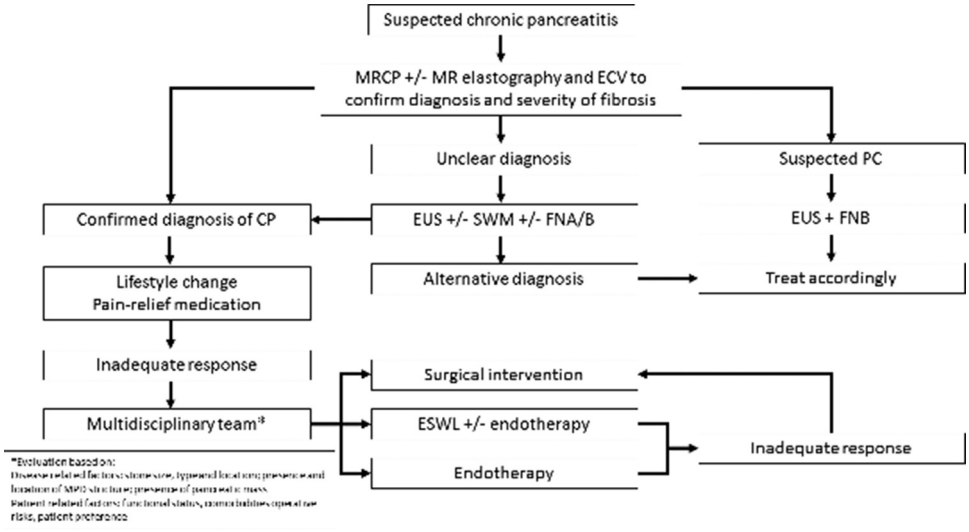

Figure 7. Proposed evidence-based algorithm for management of adult patients with chronic pancreatitis.

CP, chronic pancreatitis; ECV, extracellular volume measurement; ESWL, extracorporeal shock wave lithotripsy; EUS, endoscopic ultrasound; FNA/B, fine-needle aspiration/biopsy; MRCP, magnetic resonance cholangiopancreatography; MPD, main pancreatic duct; SWM, shear-wave measurement; PC, pancreatic cancer.

referred for treatment in expert centers, where advanced diagnostic and therapeutic modalities are readily available.

Over the following years, we expect that evidence-based algorithms are proposed and validated, with the aim of answering the following key questions: 1. Which patients should be offered endoscopic therapy and when? 2. Which type of stent(s) should be used to treat MPD strictures and for how long should the treatment last? 3. How should intraductal stones be approached? 4. How to select the best candidates for surgery? A potential algorithm for patient management in the near future is depicted in Figure 7.

Based on all the available evidence, including the large volume of original research in the field over the past few years, we believe that the field of diagnosis and treatment for CP will evolve rapidly over the next few years. New technologies will be incorporated into everyday practice and the strength of evidence backing our medical decisions will very likely increase significantly in the near future, owing to the high-quality medical research in the field.

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