27

Pancreas Divisum and Other Potential Obstructive Causes of Chronic Pancreatitis

When and How to Treat Them?

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Introduction

Pancreatic ductal obstruction is considered a cause of chronic pancreatitis (CP), presumably by inducing a persistent or transient obstruction to flow of pancreatic juice into the duodenum with a subsequent rise in intraductal pancreatic pressure. Often, it may be unclear whether an "obstructive" factor is responsible for pancreatitis or whether the etiology is idiopathic. This chapter reviews the concept of idiopathic pancreatitis (IP) before discussing potential causes of obstructive CP, divided into anatomical congenital variations of the biliopancreatic ductal system and acquired obstructive conditions at the level of the major/minor papilla. A major focus is to review the significance of the normal pancreatic ductal variant pancreas divisum, which is the focus of an ongoing multicenter trial. Other topics are subsequently discussed in an abbreviated format (Table 27.1) noting that congenital conditions that lead to pancreatic duct obstruction and pancreatitis are rare and the published literature on this topic is limited mostly to case reports or series. In most cases of obstructive pancreatitis, either endoscopic or surgical correction of the anomaly has been the general approach for treatment. A summary and clinical practice recommendations are provided in Table 27.2.

Idiopathic Pancreatitis

IP is defined as pancreatitis lacking a known association of etiological factors of acute pancreatitis (AP) and/or CP. Some factors are associated only with AP (gallstones, triglycerides, calcium, and drugs); others may be associated with both (trauma, alcohol, smoking, cancer, autoimmune, celiac disease, genetic). To emphasize, IP exists if all known associations with AP and CP are excluded and IP is CP (in early phases the patient may have attacks of pancreatitis, but if followed long enough will develop hallmarks of CP). Thus IP encompasses the diagnoses of "idiopathic acute" and "idiopathic chronic" pancreatitis used by others.

IP, so defined in the era before genetics and endoscopic ultrasound (EUS), is uncommon. Approximately 18% of patients with CP have IP based on a longitudinal study of consecutive patients (1976–1982) [1]. Other data support this generalization. After a first attack of AP, 10–20% have no cause identified with routine testing [2]. Of these, EUS identifies a cause in 80% [3]. Thus, approximately 2–4% of patients with first-attack pancreatitis have no identifiable cause, and would be considered to have IP. In other studies, it was reported that a second attack occurs in fewer than 20% [4–7]. Most have an identifiable cause, termed recurrent AP (RAP) [8–15]. Few have no identifiable cause and may be considered to have IP, or more specifically chronic relapsing pancreatitis (CRP).

To accurately label patients as IP requires adequate follow-up. Unfortunately, prospective follow-up and testing of patients is rare. Combined, the results of three careful follow-up studies [13–15] identified a cause in 50% of patients originally labeled as IP, leading to diagnoses of idiopathic CP and microlithiasis. Similar to findings of older prospective but uncontrolled studies [16,17], a randomized controlled trial from Finland suggests a biliary cause is underestimated in IP [18]. Empirical cholecystectomy for IP reduced the frequency of recurrent attacks from 50% to 20% over a median of 36 months. Most of the resected gallbladders had stones and sludge. The number needed to treat to prevent one recurrence was five.

The terminology of pancreatitis is confusing but is more understandable by applying the following four terms, as defined previously [19]: RAP, IP, CRP [20–22], and established CP (ECP) [1,23].

IP has two phenotypic expressions [1,24]: early onset at a mean age of 23 years and late onset at a mean age of 62 years. The natural history of early-onset idiopathic

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Table 27.1 Potential obstructive causes of chronic pancreatitis.[a]

Anatomical congenital variations of biliopancreatic ductal system
Pancreas divisum (± Santorinicele)
Pancreaticobiliary union (APBU)
Choledochocele
Choledochal cysts
Duodenal duplication
Periampullary diverticula
Acquired obstructive conditions at the level of major/minor papilla
(Pre)neoplastic causes
Congenital variations of the pancreaticobiliary junction
Pancreatic cancer
Ampullary adenoma/tumor
IPMN: mixed variant or main duct
Neoplastic cysts
Non-neoplastic causes
Periampullary diverticulum
Duodenal strictures at the level of the ampulla
NSAID use
Crohn's disease
Celiac disease
Radiation
Iatrogenic
Main pancreatic duct stricture
Traumatic
Post necrotizing
Postsurgical stricture (enteric ductal anastomosis)

[a] This table does not include pancreatic sphincter of Oddi dysfunction and annular pancreas due to lack of strong evidence or rarity. APBU, anomalous pancreaticobiliary union; IPMN, intraductal papillary mucinous neoplasm; NSAID, nonsteroidal anti-inflammatory drug. *Source:* adapted from Delhaye et al. [62].

Table 27.2 Summary and recommendations for clinical practice.

Idiopathic pancreatitis

Apply term "idiopathic pancreatitis" (IP) after excluding causes of AP and CP

Pancreas divisum and pancreatitis

- Evidence is insufficient to support PD as a cause of pancreatitis, based on four criteria:
  a) Prevalence of PD is similar in pancreatitis compared to no pancreatitis
  b) Most with PD lack dorsal duct dilation
  c) Pathological changes are not restricted to the dorsal duct (generalized disorder)
  d) There are no convincing data to suggest that drainage procedures of the duct of Santorini affect the frequency or severity of recurrent attacks of pancreatitis
- If PD and pancreatitis occur, consider gene mutations (e.g. *CFTR*) as a cause
- When gene mutations are found in pancreatitis and PD refer for genetic counseling
- Perform no endotherapy or surgery of sphincter for pancreatitis and PD
- Endoscopic therapy causes pancreatitis and is associated with other complications
- Ongoing randomized controlled trial aims to determine if endotherapy of accessory sphincter is beneficial

Other "obstructive" causes of pancreatitis

- Periampullary obstruction leading to pancreatitis is rare, but described with malignant, premalignant and congenital conditions
- Causes of acquired ampullary obstruction include periampullary malignancies, chronic NSAID use, Crohn's disease, and enteral stenting
- Individualized surgical, medical, and endoscopic treatment focuses on the cause of obstruction, but few outcome data are available to direct therapy

CP, in whom many now might be found to have a genetic cause and would thus no longer be classed as IP, is characterized by recurrent episodes of painful attacks at variable intervals of months to years during the early course of the disease when hallmarks of CP are not present [1,24].

There are also two phenotypes of CP.

1) CRP: the patient has relapsing pain but is not recognized clinically as having CP but does have pathological changes [20–22]. This occurs with or without the presence of known causes or risk factors such as alcohol, genetic predisposition, smoking, or prior necrotizing pancreatitis.
2) ECP: this second phenotype has at least four of the 16 points required for definite CP according to the Mayo Clinic scoring system [1,25,26].

Pancreas Divisum

Understanding the differences among RAP, IP, and phenotypes of CP (CRP, ECP) is relevant to patients with pancreatitis and pancreas divisum (PD). Up to 53% of patients with pancreatitis and PD have evidence of CP [9,27–30]. A high proportion of patients with PD and pancreatitis have gene mutations. These patients should be considered as having CP due to gene mutations.

The seventeenth century led to the discovery of normal variations of duct structures by anatomists. Among those include PD, defined as failed dorsal and ventral duct fusion during embryogenesis. As reviewed by Stern [31], Regnier de Graaf first reported this normal variation in humans in 1664, Meckel explained the origin in 1812, and Joseph Hyrtl later depicted PD and coined the term in 1859 [32]

During the second month of fetal development the pancreas results from intestinal rotation and fusion of the dorsal and ventral pancreatic buds. In PD, the two ducts fail to fuse. The dorsal duct remains and drains the majority of the pancreas via the minor papilla and the short ventral duct drains the inferior portion of the head of the pancreas.

In the 1970s, PD was increasingly identified by endoscopic retrograde cholangiopancreatography (ERCP), which led to the question of whether PD caused pancreatitis (Figure 27.1). Whether PD causes pancreatitis remains controversial.

We previously proposed that if PD causes pancreatitis, four criteria should be met (see Table 27.2). We discuss each criterion individually along with updated information.

Criterion 1: The Prevalence of PD Should be Greater in Pancreatitis than in the General Population (Figure 27.2)

We previously determined the prevalence of PD in patients with and without pancreatitis by analyzing 77 studies that fell into four categories: autopsy ($n = 23$), ERCP ($n = 41$), magnetic resonance cholangiopancreatography (MRCP) ($n = 8$), and secretin-stimulated MRCP ($n = 7$) [9]. Data for analysis was available for 54 studies ($n = 25\,872$ subjects). The prevalence of PD varied depending on the type of investigation. In autopsy and MRCP studies the prevalence was 8% in the group without pancreatitis. In contrast the prevalence in ERCP studies was 4% in the group without pancreatitis and 8% in the group with pancreatitis. These data suggest that there is no association between PD and pancreatitis and the ERCP data are due to under-recognition of PD in the general population.

Criterion 2: A Dilated Dorsal Duct System Should be Present if There is a Functionally Significant Obstruction

Most patients with PD lack a dilated dorsal duct [33–37] even when pancreatitis is associated with PD [38]. This undermines a causal relationship. A potential but flawed explanation is that the juice flow rate decreases and intraductal pressure increases but not enough to cause duct dilation [9].

Another problem is that tests do not appear specific for detecting functional obstruction of the dorsal duct [9]. A single uncontrolled surgical study suggests that reduction in duct and sphincter pressures after sphincteroplasty predicted a good outcome [39]. In contrast, secretin-stimulated ultrasound [40,41] and MRCP [42,43] evoked persistent duct dilation but is nonspecific because it occurs in 50% of controls [40] and there is no difference between patients with and without PD [40–43]. Similarly, Klein and colleagues reported in an evidence-based review that there are scant manometry data of the minor papilla but that in patients with IP and PD, results are conflicting whether readings differ at the minor versus major papilla [38,44,45].

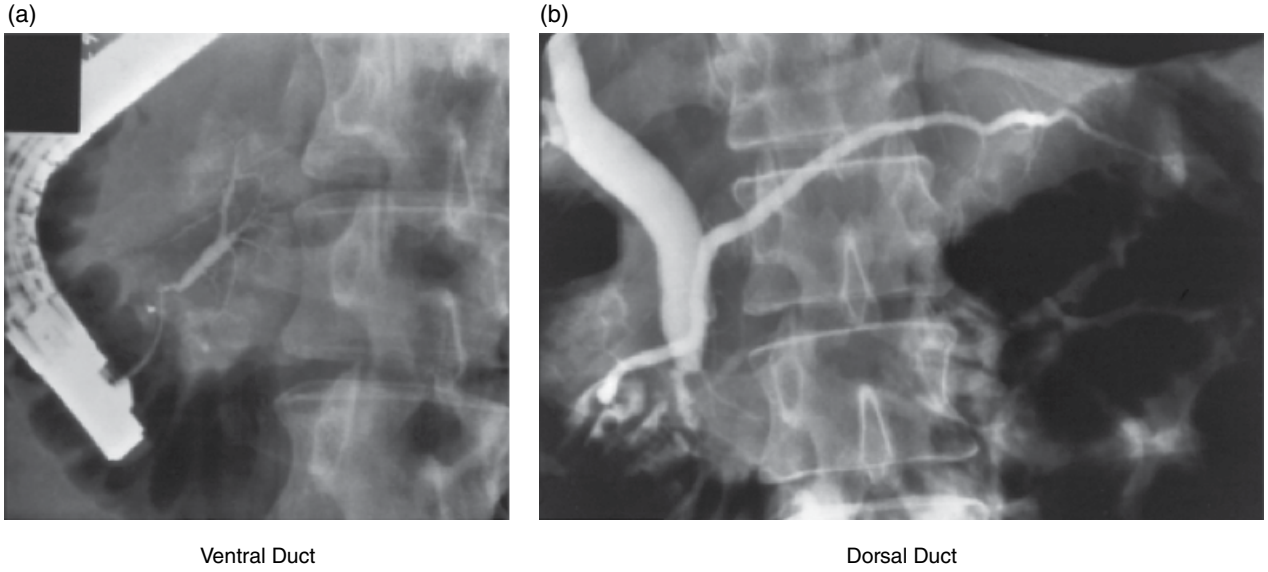

Figure 27.1 Pancreatogram in pancreas divisum (PD). (a) The pancreatogram shows the truncated but normal-appearing ventral duct in PD. (b) The normal-appearing dorsal duct from the same patient. *Source:* adapted from DiMagno and DiMagno [9]. Reproduced with permission of Wolters Kluwer.

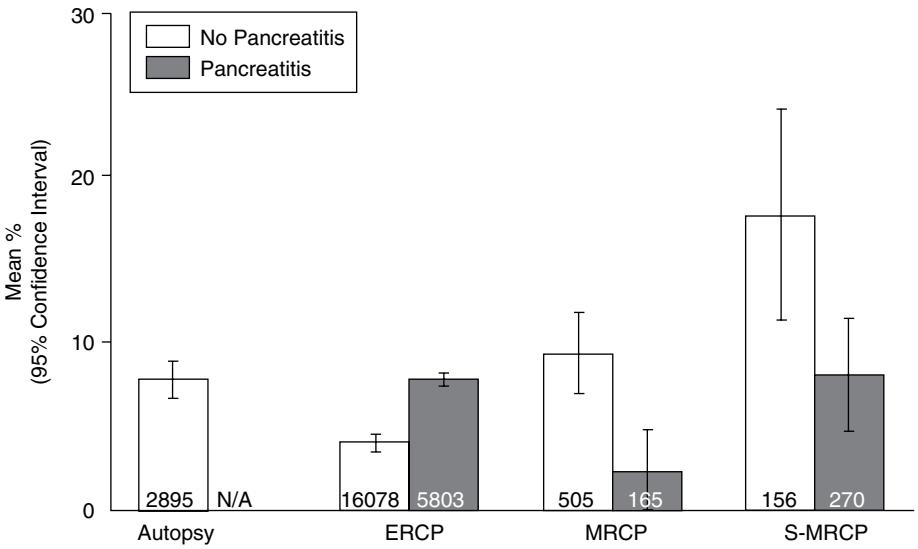

Figure 27.2 Prevalence of pancreas divisum (PD) is no greater in patients with pancreatitis versus those without pancreatitis. Mean prevalence and 95% confidence interval for PD is shown for each of four groups. Subgroups of no pancreatitis (white bar) and pancreatitis (gray bar) are provided for each of the four groups except autopsy, which lacked a pancreatitis group (largely because these studies were intended to classify normal variations of human pancreatic ducts and structures). *Source:* adapted from DiMagno and DiMagno [9]. Reproduced with permission of Wolters Kluwer.

In a German population-based study of 927 volunteers, investigators determined that exocrine pancreatic function was not reduced in those with PD [46]. Subjects underwent secretin-stimulated MRCP and total body magnetic resonance imaging (MRI); 10% had PD, similar to the pooled analysis by DiMagno and DiMagno [9]. Importantly, the authors reported that pancreatic volume output (measured by secretin-stimulated MRCP) was similar in persons with PD and persons with normal ductal anatomy. This weakens arguments about an outflow obstruction in PD. Similarly, there was no significant difference in three morphological features that can associate with CP.

Criterion 3: Pathological Changes Should Develop only in the Dorsal Duct

In patients with PD and pancreatitis (pooled data from ERCP, MRI, and autopsy studies) [9], 61% have normal ducts (or not reported), 23% have pancreatitis in the dorsal pancreas, 12% have dorsal and ventral disease, and 4.2% have only ventral disease. In the latter, many develop dorsal duct disease over time. The conclusion is that the presence of disease in both ventral and dorsal pancreas indicates that factor(s) other than PD are responsible for pancreatitis (and a generalized pancreatic disorder). A weak argument is that pancreatitis originates in the dorsal duct and spreads to the ventral pancreas but this does not explain why some have pancreatitis only of the ventral duct.

Criterion 4: Drainage Procedures of the duct of Santorini Should Reduce the Frequency or Severity of Recurrent Attacks of Pancreatitis

A fundamental challenge when interpreting the literature of endoscopic therapy for the treatment of pancreatitis in PD is that it is difficult to assess a true response to medical, endoscopic, and surgical treatment of pancreatic disorders in the absence of a placebo/sham control arm. To report the effectiveness of drainage procedures, we have assessed NIH consensus comments [47], a systematic review [48], a single randomized controlled trial study by Lans et al. [49], and a review of the placebo response [50].

The 2002 NIH Consensus [9,47] ". . .suggested that ERCP treatment with stent or sphincterotomy decreases recurrent . . . pancreatitis and reduces pain . . . a single trial (supports) . . . but further research is warranted." An area of concern is the complications of ERCP, which are increased significantly in patients with PD, including post-ERCP pancreatitis in 18% (148/818), papillary restenosis in 11% (66/619), hemorrhage in 1% (10/734), and potentially stenting-induced ductal features of CP [48]. These complications can be prevented by avoiding unnecessary ERCP.

As a follow-up to a 2009 systematic review by Liao et al. [51], Kanth et al. [48] evaluated 22 studies focused on endoscopic therapy for PD in IP and used three categories of pancreatitis (Table 27.3). The main message is that there appears to be a numerically higher response to endotherapy in the acute recurrent pancreatitis (ARP) group compared to the other groups, although the extreme overlap (reported as

Table 27.3 Endoscopic therapy in pancreatitis and pancreas divisum: systematic review.

Group	*n*	Median response to therapy	Range
Acute recurrent pancreatitis (ARP)	314	76%	43–100%
Chronic pancreatitis (CP)	173	42%	21–80%
Chronic abdominal pain (CAP)	97	33%	11–55%

Source: data from Kanth et al. [48].

range rather than confidence intervals) suggests there is no significant difference. Moreover, this systematic review is limited by analysis of only a single placebo/sham-controlled trial [49] and by including heterogeneous patients, treatments, and definitions. It is also unclear whether the patients with ARP and CP had RAP or CRP.

The study by Lans et al. [49] focused on 19 patients with pancreatic pain (without necessarily meeting standard criteria for pancreatitis) and PD. Patients were randomized to ERCP or ERCP plus pancreatic duct stenting for one year. The stenting group had better outcomes at one year in terms of the total number of attacks and hospitalizations and more patients that had symptom improvement (measured by visual analog scale). Significant limitations were multiple, and raise concerns about data interpretation, including (i) patients did not meet standard criteria for pancreatitis; (ii) the study was unblinded (endoscopists assessed response); and (iii) small study size and short one-year follow-up.

In a meta-analysis of the medical placebo response in patients with abdominal pain in CP, the pooled estimate for a placebo response was 20%, with a 95% confidence interval of 10–36 [50]. It is noteworthy that this placebo response is very similar to the placebo response in a multicenter octreotide randomized controlled trial [52,53], which has been published only in abstract form, and the 32% response to endoscopic therapy in a separate randomized controlled trial that focused on patients with painful CP. Data from the study by Cahen et al. [54,55] suggest that the response to endotherapy was a placebo rather than a response to treatment whereas the 75% response to modified Puestow surgery was due to treatment.

We need randomized controlled trials of sufficient sample size and duration to determine if endotherapy or surgery of the accessory sphincter is beneficial. Fortunately, the NIH has awarded funding for such an effort, led by Dr. Gregory Cote and colleagues, entitled SpHincterotomy for Acute Recurrent Pancreatitis (SHARP) (Clinicaltrials.gov. NCT03609944).

Alternate Genetic Explanations for Pancreatitis and PD

Several studies that employed genetic testing provided an alternate explanation for IP in patients with PD. Two studies suggested that *SPINK1* and *CFTR* gene mutations associate with IP independently of the presence of PD. First, Garg et al. [56] reported that the prevalence of *SPINK1* mutations was similarly increased in patients with IP and PD (41.6%) and RAP without PD (35.7%) compared with healthy controls (2%). Choudari et al. [57] reported a similar prevalence of *CFTR* gene mutations (detected using a limited screening panel) in patients with IP and PD (22%) compared to those with IP without PD (19%). These data would suggest that PD is not a cause of pancreatitis but rather that patients with PD and pancreatitis have CP due to *CFTR* or other mutations (*PRSS1*, *SPINK1*).

Data from Bertin et al. of 114 consecutive patients with IP or of genetic etiology support an alternate, genetic explanation for pancreatitis associated with PD [11,58]. These data are reconstructed in (Table 27.4). The first message is that 65% of patients with pancreatitis have any of three gene mutations, supporting the concept that they have CRP. A second message is that the proportion of gene mutations increases to over 90% in the subgroup with pancreatitis and PD. Thirdly, in the subgroups with pancreatitis, *CFTR* mutations were more common in the presence rather than absence of PD. Lastly, the data can be interpreted as indicating that PD and *CFTR* mutations may comingle in pancreatitis but PD is not necessary for pancreatitis to develop.

Other Potential Obstructive Causes of Chronic Pancreatitis

This section is divided into (pre)neoplastic and non-neoplastic etiologies. A limitation of the following sections is that in many instances the type of pancreatitis (discussed in the section on IP) is unclear and is not necessarily CP.

(Pre)Neoplastic Causes

Anatomical Congenital Variations Affecting the Biliopancreatic Ductal System

In the case of choledochal cysts, type III choledochal cysts (also known as choledochoceles) frequently present with pancreatitis due to pancreaticobiliary outflow obstruction, intracystic stone formation, or extrinsic compression onto the ampulla. Other choledochal cysts present with pancreatitis much less frequently [59].

Duplication cysts are benign congenital anomalies that can occur anywhere in the gastrointestinal tract and consist

Table 27.4 *CFTR* mutation frequency is higher in pancreatitis patients with PD compared to those without PD.[a]

Pancreatitis	PD	Mutations	Percent	*n*
Yes	All patients	*PRSS1/SPINK1/CFTR*	65	(74/114)
Yes	Yes	*PRSS1/SPINK1/CFTR*	91	(21/23)
		PRSS1	13	(3/23)
		SPINK1	17	(4/23)
		CFTR	61	(14/23)
Yes	No	*PRSS1/SPINK1/CFTR*	58	(53/91)
		PRSS1	18	(16/91)
		SPINK1	23	(21/91)
		CFTR	18	(16/91)
No	Yes	None	7	(3/45)

[a] Consecutive patients with idiopathic pancreatitis or genetic etiology (2000–2008).
CFTR, cystic fibrosis transmembrane conductance regulator; PD, pancreas divisum. *Source:* adapted from Bertin et al. [58].

of the mucosa and an outer smooth muscle wall layer. Periampullary duplication cysts can compress the pancreatic duct system leading to pancreatitis. Traditional treatment involves complete surgical resection or partial resection in combination with cyst drainage [60] but endoscopic submucosal dissection techniques have also been increasingly utilized to incise and drain the duplication cyst [61].

Acquired Obstructive Conditions

Several neoplastic causes of pancreatic duct obstruction may lead to pancreatitis: primary pancreatic cancer, ampullary and pancreatic neuroendocrine tumors, ampullary adenocarcinoma, pancreatic metastases, and intraductal papillary mucinous neoplasm (IPMN) [62]. It is unclear why some tumors cause pancreatic duct obstruction but do not cause pancreatitis, but this is perhaps related to the rapidity of obstruction or tumor infiltration. Although uncommon, pancreatitis is an established initial presentation of pancreatic cancer. Hence, unexplained pancreatitis should prompt imaging in selected patients with risk factors, such as age greater than 40 years [63]. IPMN presents with AP in 12–67% in surgical series, with no apparent difference in rates between benign and malignant subtypes [64]. Despite conflicting older literature, more recent surgical series show a stronger association of AP with the main-duct IPMN intestinal epithelial subtype, which produces highly viscous glycoproteins and functional obstruction of the pancreatic duct [65]. Guidelines generally recommend surgical resection in patients with symptomatic IPMN.

Other epithelial pancreatic cysts (mucinous cystic neoplasms, serous cystadenomas, cystic lymphangiomas) have been rarely reported to cause AP [66–68]. In these cases, compression on the main pancreatic duct has been noted on imaging leading to partial pancreatic duct obstruction, the presumed cause of pancreatitis.

Non-neoplastic Causes

Periampullary Obstruction: Duodenal Diverticula and Other Causes of Periampullary Obstruction

Duodenal diverticula have been reported in up to 7% of patients undergoing ERCP and 2–5% of patients undergoing upper gastrointestinal series [69] and in up to 22% at autopsy. Few case reports are available that implicate periampullary diverticula as a cause of AP. Potential mechanisms for pancreatitis involve partial obstruction of the pancreatic duct at the level of the ampullary orifice and the neck of the diverticulum, inspissated food partially obstructing the outflow from the ampulla, and potentially other causes [70].

Our thorough review of the literature has identified several benign and uncommon causes of obstruction at the level of the ampulla that may lead to obstructive pancreatitis: chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs), Crohn's disease, celiac disease, radiation therapy, and iatrogenic ampullary obstructions. Chronic NSAID use, Crohn's disease, and celiac disease may cause obstructive pancreatitis from stricture development at the level of the ampulla [71,72]. Reducing exposure to NSAIDs and medical treatment of Crohn's and celiac disease are the primary therapies, but data are limited due to the rarity of these conditions. Radiation therapy is known to cause AP and CP [73], but pancreatic complications may be blunted by advances in radiation therapy allowing for reduced radiation exposure of the pancreas. Ampullary compression by a palliative duodenal stent (for malignant obstruction) may cause obstructive AP in 4.1% of patients. It is unclear,

however, whether CP ensues due to the shortened lifespan of this generally terminal population [74]. Conceivably, preprocedural biliary stenting may prevent compression of the ampulla and reduce the risk of obstructive AP.

Main Pancreatic Duct Stricture

Both penetrating and blunt abdominal injuries can result in pancreatic trauma. A late complication of pancreatic trauma is felt to be due to main pancreatic duct injury. Pancreatic leaks that are limited to pancreatic duct side branches or partial main pancreatic duct disruptions may be successfully treated with endoscopic transpapillary stent placement and those with complete disruptions are treated surgically [75,76]. In patients with main pancreatic duct injury but without complete disruption, this uncommon complication may best be treated surgically [75]. There are scant data on long-term outcomes of patients treated acutely with endoscopic stent placement.

Necrotizing pancreatitis is a common cause for partial and complete pancreatic duct obstructions. In surgical series, 14–38% of patients with necrotizing pancreatitis develop either a high-grade pancreatic duct stricture or a complete pancreatic duct cutoff, predisposing to recurrent pancreatitis and pancreatic pseudocyst formation [77,78]. Most of these patients are treated with surgical resection (disconnected pancreatic duct) or endoscopic stent placement or EUS-guided pancreatic fluid collection drainage.

Postsurgical Pancreatic Duct Stricture

Pancreatic resections are increasingly performed for benign (e.g. CP) and malignant reasons. As long-term survival from these operations is improving, late complications of anastomotic strictures are increasingly being recognized and reported. A recent systematic review of pancreaticojejunostomy anastomotic strictures observed an incidence up to 11.4%, complicated by chronic abdominal pain, RAP, and/or pancreatic endocrine and exocrine insufficiency [79]. The primary indications for treatment are pain and pancreatitis. Endoscopic stenting and dilation of the anastomotic stricture has been proposed, but anatomical issues contribute to low success rates unless a combined approach is used involving EUS and ERCP rendezvous techniques. As a last resort, surgical revision of the anastomosis may be considered.

Postsurgical Intestinal Obstruction

Afferent loop obstruction is another surgical complication that can lead to pancreatic duct obstruction and AP. Over time, accumulation of pancreaticobiliary secretions in the afferent limb can lead to cholangitis and pancreatitis. This complication is most commonly seen after total gastrectomy with Roux-en-Y reconstruction, Billroth II partial gastrectomy with Roux-en-Y reconstruction, and pancreaticoduodenectomy with conventional loop or Roux-en-Y reconstruction. Treatment is surgical unless the obstruction is due to recurrent malignancy where the preference is to treat with enteral stent placement [80].

Pancreatic Sphincter of Oddi Dysfunction

This topic is not discussed due to the lack of clinical data supporting a role for pancreatic sphincter of Oddi dysfunction as an etiological factor in CP.

Disclosures

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