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Review article

Endotherapy in symptomatic pancreas divisum: A systematic review☆

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ABSTRACT

Pancreas divisum (PD) is the most common congenital variant of the pancreas and has been implicated as a cause of pancreatitis; however, endoscopic treatment is controversial. Our objective was to examine patient response to endotherapy for treatment of symptomatic PD in adult patients in a systematic review of the literature. A systematic review of all case series and case–control studies with ten or more patients undergoing endotherapy for treatment of symptomatic PD indicated by acute recurrent pancreatitis (ARP), chronic pancreatitis (CP), or chronic abdominal pain (CAP) was performed. PubMed, Embase, and Web of Science databases were searched from inception through February 2013 using [pancreas divisum] AND [endoscopic retrograde cholangiopancreatography (ERCP)] OR [endotherapy] OR [endoscopy] as search terms. Importantly, the majority of studies were retrospective in nature, significantly limiting analysis capacity. Main outcomes measures included endotherapy response rate in patients with PD and ARP, CP, or CAP. Twenty-two studies were included in the review, with a total of 838 patients. Response to endoscopy was seen in 528 patients, but response rate varied by clinical presentation. Patients with ARP had a response rate ranging from 43% to 100% (median 76%). Reported response rates were lower in the other two groups, ranging from 21% to 80% (median 42%) for patients with CP and 11%–55% (median 33%) for patients with CAP. Complications reported included perforation, post-endoscopic retrograde cholangiopancreatography pancreatitis, bleeding, and clogged stents. Endotherapy appears to offer an effective treatment option for patients with symptomatic PD, with the best results in patients presenting with ARP.

1. Introduction

Pancreas divisum (PD) is the most common congenital variant of the pancreas with an overall prevalence of approximately 2.9% [1], although detection rates vary from 4% to 10% in Caucasian populations and 1%–2% in Asian populations [1–3]. PD occurs due to failure of embryological dorsal and ventral pancreatic duct fusion at 6–8 weeks gestation [4]. Many studies suggest that PD has an etiological role in idiopathic pancreatitis [5–7]. However, the clinical significance of PD is debated, as most patients are asymptomatic, and less than 10% develop pancreatitis [8–10]. Recent studies indicate that genetic mutations, particularly in the *CFTR* gene, may be associated with a predisposition to pancreatitis in patients with PD [11–13]. This genetic susceptibility may explain why some patients with PD get pancreatitis and others do not [14,15].

The pathogenesis of pancreatitis in PD is thought to be secondary to minor papilla stenosis, which causes resistance to the flow of pancreatic secretions and leads to increased intraductal pressure. Based on this pathophysiology, endoscopic or surgical minor papilla ductal decompression is used to treat idiopathic pancreatitis or chronic abdominal pain associated with PD. Several methods of endoscopic therapy are commonly used, including minor papillotomy (needle-knife sphincterotomy over a stent or pull-type sphincterotomy), stent placement, and balloon dilation of the minor papilla. Although endotherapy is commonly used for the

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Abbreviations

ARP	acute recurrent pancreatitis
CAP	chronic abdominal pain
CP	chronic pancreatitis
ERCP	endoscopic retrograde cholangiopancreatography
PD	pancreas divisum

treatment of symptomatic PD, it is controversial, and the outcome of treatment is debated. The purpose of this systematic review was to assess patient response to endotherapy for the treatment of symptomatic PD with acute recurrent pancreatitis, chronic pancreatitis, or chronic abdominal pain in published case-series and case–control studies including at least ten unique patients.

2. Methods

2.1. Study selection

All articles assessing the effectiveness of endotherapy in pancreas divisum in adult patients were selected, and studies with a sample size of ten or more adult patients were included. Studies describing surgical intervention for PD, letters, editorials, and reviews were excluded from analysis. There were no language restrictions. Both full-length and abstract publications were included in the study.

2.2. Literature search

A literature search was conducted to identify relevant original articles related to PD and endotherapy. PubMed, Embase, and Web of Science databases were searched from inception through February 2013 using [pancreas divisum] AND [endoscopic retrograde cholangiopancreatography (ERCP)] OR [endotherapy] OR [endoscopy] as search terms. After excluding duplicate records, we scanned titles and abstracts to determine the relevance of content and then retrieved full texts of potentially relevant articles for detailed evaluation. We also manually searched the bibliographies of extracted manuscripts for relevant references.

2.3. Data extraction process

Data extraction was performed by two authors independently. Information regarding study design, sample size, patient demographics, interventions (endotherapy), outcomes (response to treatment), and adverse events of endotherapy (haemorrhage, perforation, clogged stent, and stent migration) was extracted using a standardized form. Results were compared and discrepancies resolved through discussion. Endotherapy was defined as endoscopic minor papilla sphincterotomy, stenting, or dilation. In most studies, subjects were subdivided into three or more categories based on indication for PD endotherapy. For the purposes of this review, we considered only those patients with symptomatic PD treated by endotherapy for (1) acute recurrent pancreatitis, (2) chronic pancreatitis, and (3) chronic abdominal pain. Case definitions of acute recurrent pancreatitis, chronic pancreatitis, and chronic abdominal pain in patients with pancreatic divisum were used as described in the original report. In the studies included, acute recurrent pancreatitis (ARP) was usually defined as acute pancreatitis on more than one occasion with elevated serum lipase and amylase in the absence of imaging evidence of chronic pancreatitis. Chronic pancreatitis (CP) was diagnosed based on ductal dilatation, strictures, irregularity identified by dorsal ductography, or other imaging evidence (e.g., calcification, pseudocyst). Chronic abdominal pain (CAP) was most often defined as a pain syndrome consistent with pancreatitis but without identifiable etiological cause. Usually, serum lipase and amylase are not elevated in the context of CAP, and imaging studies do not reveal any abnormalities. The number of patients with PD undergoing endotherapy varied by the indication for ERCP. Only those patients with ARP, CP, or CAP as the indication for endotherapy in the context of PD were included in the current study. Patients with different indications for endotherapy (e.g., periampullary mass), in whom endotherapy was unable to be performed, who were lost to follow-up, and those with pancreatitis who did not undergo endotherapy were excluded from analyses.

Similar to definitions for endotherapy indication, the criteria used to define endotherapy success also varied by study. Therefore,

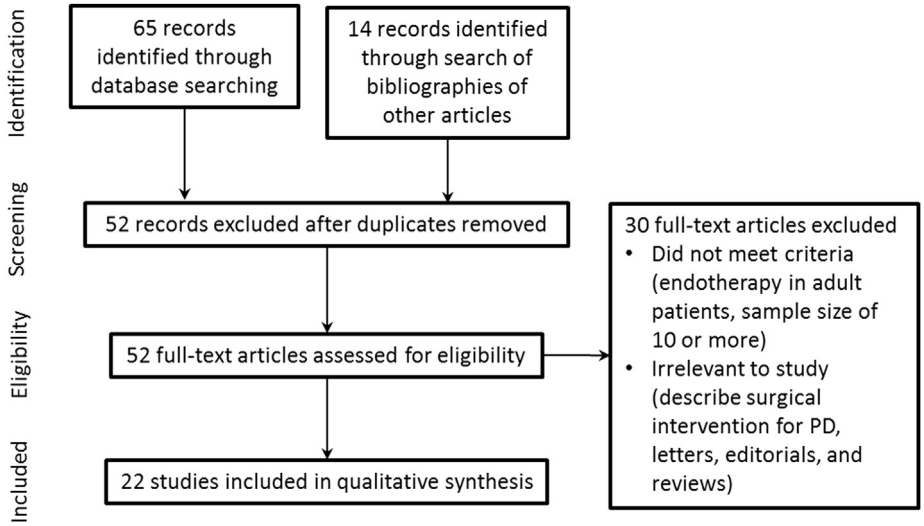

Fig. 1. PRISMA flow diagram describing literature search for relevant studies. The PubMed, Embase, and Web of Science databases were search from inception through February 2013 using [pancreas divisum] AND [endoscopic retrograde cholangiopancreatography (ERCP)] OR [endotherapy] OR [endoscopy] as search terms and studies were selected as shown.

Table 1
Publications describing endotherapy success for symptomatic pancreas divisum.

Reference	Country	Study design	Definition of response to endotherapy
Definition of response to endotherapy includes at least one objective measure of pancreatitis			
McCarthy et al., 1988 [36]	USA	Prospective	Decreased frequency of attacks of pain and emergency admission
Satterfield et al., 1988 [37]	USA	Retrospective	Significant reduction in linear ranking pain scale score and number of hospitalizations for pancreatitis or abdominal pain after endotherapy
Lehman et al., 1993 [33]	USA	Prospective	Symptomatic improvement as defined by symptom score decrease to 0 or 2 based on pain severity, narcotic requirement, number of episodes of pancreatitis or pain requiring hospitalization or emergency department visits
Chacko et al., 2008 [22]	USA	Retrospective	For patients with ARP: ≥50% reduction in annual acute pancreatitis episodes, emergency department visits, or hospitalizations. For patients with CP or CAP: ≥50% reduction in pain score, use of narcotic analgesia, annual emergency department visits, or hospitalizations.
Lans et al., 1992 [34]	USA	Prospective	Patient rating of ≥50% improvement after endotherapy considering number of hospitalizations and/or emergency room visits for abdominal pain, number of documented episodes of acute pancreatitis, and overall general feeling graded on a visual analogue scale
Catalano et al., 2009 [19]	USA	Retrospective	Reduction in the occurrence of acute pancreatitis by >50%
Di Leo et al., 2010 [18]	Italy	Retrospective	Absence of further recurrence after endoscopic therapy
Kwan et al., 2008 [21]	Australia	Retrospective	Complete abolition of pancreatitis episodes during follow-up
Ertan et al., 2000 [27]	USA	Prospective	Remains symptom free without requirement for hospitalization or emergency room visit for abdominal pain or recurrent pancreatitis during follow-up
Jacob et al., 1999 [29]	USA	Retrospective	No recurrence of pancreatitis or pancreatic-type pain
Definition of response to endotherapy requires no further treatment or intervention			
Vitale et al., 2007 [23]	USA	Retrospective	Required no further treatment after endoscopic therapy
Attwell et al., 2006 [24]	USA	Retrospective	No need for any reintervention
Definition of response to endotherapy relies on patient perception of pain and/or therapy efficacy			
Borak et al., 2009 [20]	USA	Retrospective	Clinical improvement (better or cured on Likert scale) without narcotics after one ERCP
Gerke et al., 2004 [25]	USA	Retrospective	No symptoms or minimal symptoms (≤2 on visual analogue scale from 0 to 10) after endoscopy with no recurrence of symptoms or symptoms that resolved after repeat endoscopy
Heyries et al., 2002 [26]	France	Retrospective	Suppression or a decrease in perception of acute pancreatitis and improvement or absence of pain as measured by the consumption of analgesic drugs
Boerma et al., 2000 [28]	Netherlands	Retrospective	Remain pain-free during follow-up
Kozarek et al., 1995 [30]	USA	Retrospective	Patient overall interpretation of significant response (global improvement) to endotherapy
Cohen et al., 1995 [31]	USA	Retrospective	Patients who rated response to endotherapy as "much better" or "completely better"
Coleman et al., 1994 [32]	USA	Retrospective	Improvement in pain scores
Siegel et al., 1990 [35]	USA	Prospective	Improvement in all signs and symptoms associated with pancreatitis
Definition of response to endotherapy not well-defined			
Rustagi et al., 2013 [16]	USA	Retrospective	Not defined in report; authors refer to "response rate"
Yamamoto et al., 2010 [17]	Japan	Retrospective	Symptom improvement, not further defined

for analysis of response rate, we again relied on the definition as described in the original report. Definitions of response to endotherapy were heterogeneous and included a decrease in episodes of pancreatitis, hospitalization, abdominal pain, narcotic use, or no need for further surgical intervention. A 2009 systematic review of endotherapy for pancreas divisum by Liao et al. [1] used a similar mechanism for defining response to endotherapy.

3. Results

Twenty-two studies [16–37] met criteria for inclusion in our review (Fig. 1), the designs of which are summarized in Table 1. Studies were reported from the United States ($n = 17$), The Netherlands ($n = 1$), France ($n = 1$), Italy ($n = 1$), Australia ($n = 1$), and Japan ($n = 1$). Seventeen studies were retrospective and five were prospective. All studies were case series studies with the exception of a single randomized, controlled trial by Lans et al. published in 1992 [34]. The retrospective nature of most studies included significantly limited capacity for analysis. Included studies varied widely in definition of response to endotherapy. We broadly characterized these definitions into four groups, including those that defined endotherapy response using at least one objective measure of pancreatitis, required no further treatment or intervention, or relied on patient perception of pain and/or therapy efficacy as well as those in which the definition of response to endotherapy was not well-defined.

Overall study characteristics are reported in Table 2. Mean patient age ranged from 33 to 52 years. A total of 838 patients with symptomatic PD underwent endotherapy as indicated by ARP, CP, or CAP. A response to endotherapy was noted in 528/838 cases, and the overall response rate to endotherapy ranged from 31% to 92% among the studies. The type of endoscopic procedures performed varied by study. Minor papilla sphincterotomy was described in 645 cases (16 studies), a minor papilla stent was placed in 594 cases (18 studies), and minor papilla balloon dilation was performed in 90 cases (9 studies). Several cases underwent both sphincterotomy and stent placement. In some instances, the exact number of cases that underwent endoscopic intervention was not documented. Stent exchange within 3–12 months and repeat sphincterotomy were described in several studies. Follow-up time after endotherapy ranged from 14 to 64 months.

The overall estimated response rate for endotherapy in patients with PD ranged from 31% to 92% with a median response rate of 62%. Response rate varied by indication for endoscopic therapy (Table 3, Fig. 2). No clear pattern in reported response rate was observed by definition of response used. In 411 patients with PD

Table 2
Patient characteristics and response rate for published studies describing endotherapy for symptomatic pancreas divisum.

Reference	Total patients	Age, y	Male	Female	Endotherapy[a]	Response to endotherapy, *N* (%)[b]	Follow-up, mo
Definition of response to endotherapy includes at least one objective measure of pancreatitis							
McCarthy et al., 1988 [36]	22	–	–	–	22	17 (77)	14
Satterfield et al., 1988 [37]	82	–	–	–	10	6 (60)	19
Lehman et al., 1993 [33]	52	44.5	13	39	52	22 (42)	20.4
Chacko et al., 2008 [22]	57	47	17	40	48	26 (54)	20
Lans et al., 1992 [34]	10	49.7	5	5	10	9 (90)	28.6
Catalano et al., 2009 [19]	31	45.8	7	24	31	25 (81)	–
Di Leo et al., 2010 [18]	34	51.8	10	24	20	14 (70)	–
Kwan et al., 2008 [21]	21	33	14	7	21	13 (62)	38
Ertan et al., 2000 [27]	25	41.5	15	10	25	19 (76)	24
Jacob et al., 1999 [29]	32	42	24	8	18	11 (34)	15.5
Definition of response to endotherapy requires no further treatment or intervention							
Vitale et al., 2007 [23]	32	43.8	7	17	24	13 (54)	59.6
Attwell et al., 2006 [24]	184	45	65	119	184	133 (72)	60
Definition of response to endotherapy relies on patient perception of pain and/or therapy efficacy							
Borak et al., 2009 [20]	113	48.6	33	80	113	70 (62)	43
Gerke et al., 2004 [25]	53	50	19	34	53	17 (32)	29
Heyries et al., 2002 [26]	24	43	16	8	24	22 (92)	39
Boerma et al., 2000 [28]	16	38	8	8	16	5 (31)	51
Kozarek et al., 1995 [30]	39	–	–	–	39	18 (46)	20
Cohen et al., 1995 [31]	20	43.3	7	13	18	9 (50)	–
Coleman et al., 1994 [32]	34	46	26	8	34	21 (62)	23
Siegel et al., 1990 [35]	31	35	5	26	31	26 (84)	24
Definition of response to endotherapy not well-defined							
Rustagi et al., 2013 [16]	45	50	20	25	33	25 (76)	–
Yamamoto et al., 2010 [17]	12	–	–	–	12	7 (58)	64

–, not reported.
[a] Total number of patients with symptomatic PD who underwent endotherapy indicated by acute recurrent pancreatitis (ARP), chronic pancreatitis (CP), or chronic abdominal pain (CAP).
[b] Response as defined by authors of original study (see Table 1 for more detail).

and ARP, endotherapy outcomes were documented for 314 patients (16 studies), with a response noted in 230 patients. The response rate of endotherapy for ARP ranged from 43% to 100%, and the median response rate was 76%. In 259 patients with PD and CP, endotherapy outcomes were documented in 173 patients (12 studies), with a response noted in 76 patients. The response rate of endotherapy for CP ranged from 21% to 80%, and the median response rate was 42%. In 135 patients with PD and CAP, endotherapy was documented in 100 patients (9 studies), with a response noted in 39 patients. The response rate of endotherapy for CAP ranged from 11% to 55%, and the median response rate was 33%.

Few studies documented technical success of the endotherapy procedure, but descriptions of sphincterotomy and/or stent placement suggest that technical success was high in such studies. In the four studies that documented technical success, success was reported in approximately 83% of procedures, but ranged from 16% to 86% depending on the study (Table 4). The most frequently reported acute and chronic procedure-related adverse events included pancreatitis, haemorrhage, papillary restenosis, and clogged stent (Table 4). Most cases of pancreatitis were self-resolving ($n = 132$), however, 15 were documented to be moderate and one case was severe. In some cases, type of pancreatitis was not documented or was considered secondary to clogged stent, in which case the stent was exchanged. In addition, stent migration occurred in at least 13 cases and perforation was reported in 2 patients.

A formal assessment of risk of bias was not performed due to the uncontrolled nature of the vast majority of studies included, with the exception of that by Lans et al. [34] Case series tend to be more prone to several types of bias, including performance, attrition, detection, and reporting bias, compared to controlled studies. Major differences in the way response to endotherapy was defined precluded a formal meta-analysis, but assessment of the results by type of definition did not reveal any clear pattern in outcomes.

4. Discussion

Although PD was first described more than a century ago, detection only increased after the advent of ERCP in the 1970s [38,39]. Approximately 1%–10% of the population has PD [1–3], but evidence suggests that only 10% of patients with PD experience symptoms [4], and the role of PD in the aetiology of pancreatitis is debated [8–10].

PD results from failure of fusion of the dorsal and ventral pancreatic ductal system at 6–8 weeks of gestation and can be categorized as either classical or incomplete PD, depending on whether failure to fuse is complete or partial, respectively. Several studies have demonstrated increased prevalence of pancreatitis in patients with PD [38,40,41]. In PD, pancreatic drainage occurs mainly through the minor papilla. Due to its small size, active pancreatic secretion through the minor papilla may result in relatively high intrapancreatic dorsal duct pressure and pancreatitis or abdominal pain [42–46]. Based on this pathophysiology, endoscopic or surgical decompression of the minor papilla is used to treat symptomatic PD [47].

The majority of patients with symptomatic PD are categorized into one of three categories: ARP, CP, and CAP. We performed a systematic review of the literature to assess the effectiveness of endotherapy for the treatment of patients with symptomatic PD in these three groups. Our systematic review found that endotherapy appears to be most successful in patients with PD and ARP, regardless of the definition of endotherapy response used, with response to endotherapy reported in a median of approximately

Table 3
Response to endotherapy in patients with symptomatic pancreas divisum by indication for procedure.

Reference	ARP		CP		CAP	
	Total	Response, *N* (%)[a]	Total	Response, *N* (%)[a]	Total	Response, *N* (%)[a]
Definition of response to endotherapy includes at least one objective measure of pancreatitis						
McCarthy et al. [36]	19	–	–	–	3	–
Satterfield et al. [37]	6	6 (100)	4	0	0	0
Lehman et al. [33]	17	13 (76)	11	3 (27)	24	6 (25)
Chacko et al. [22]	21	16 (76)	19	8 (42)	6	2 (33)
Lans et al. [34]	10	9 (90)	0	0	0	0
Catalano et al. [19]	19	17 (89)	12	8 (75)	0	0
Di Leo et al. [18]	20	14 (70)	0	0	0	0
Kwan et al. [21]	21	13 (62)	0	0	0	0
Ertan et al. [27]	25	19 (76)	0	0	0	0
Jacob et al. [29]	10	6 (60)	5	4 (80)	3	1 (33)
Category subtotal[b]	149	119 (76)	51	23 (58)	33	9 (33)
Definition of response to endotherapy includes no further treatment or intervention						
Vitale et al. [23]	0	0	24	13 (54)	0	0
Attwell et al. [24]	69	–	83	–	32	–
Category subtotal[b]	0	0	24	13 (54)	0	0
Definition of response to endotherapy relies on patient perception of pain and/or therapy efficacy						
Borak et al. [20]	62	44 (71)	22	10 (45)	29	16 (55)
Gerke et al. [25]	30	13 (43)	14	3 (21)	9	1 (11)
Heyries et al. [26]	24	22 (92)	0	0	0	0
Boerma et al. [28]	0	0	16	5 (31)	0	0
Kozarek et al. [30]	15	11 (73)	19	6 (32)	5	1 (20)
Cohen et al. [31]	7	3 (43)	0	0	11	6 (54)
Coleman et al. [32]	9	7 (78)	20	12 (60)	5	2 (40)
Siegel et al. [35]	–	–	–	–	–	–
Category subtotal[b]	147	98 (72)	91	36 (32)	56	26 (40)
Definition of response to endotherapy not well-defined						
Rustagi et al. [16]	18	17 (94)	7	4 (57)	8	4 (50)
Yamamoto et al. [17]	9	–	3	–	–	–
Category subtotal[b]	18	17 (94)	7	4 (57)	8	4 (50)
Total[b]	**314**	**234 (76)**	**173**	**76 (42)**	**97**	**39 (33)**

ARP, acute recurrent pancreatitis; CP, chronic pancreatitis; CAP, chronic abdominal pain; –, not reported.
[a] Success as defined by authors of original study.
[b] Total number of cases reported with outcome defined (i.e. excluding those where rate of success was not reported). Number in parentheses represents median response rate.

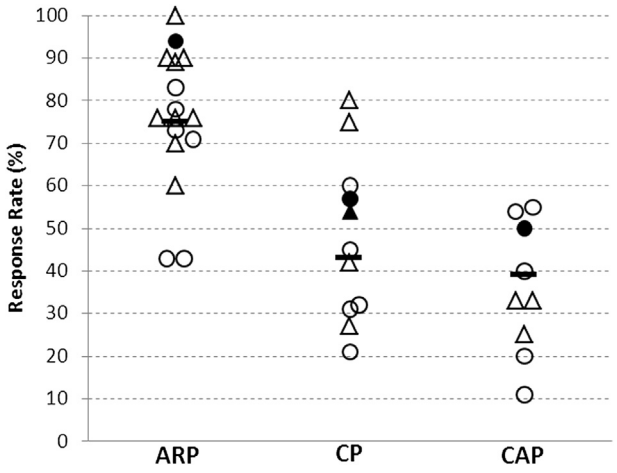

Fig. 2. Endotherapy response rate by indication for procedure. The rate of endotherapy success in patients with pancreas divisum and acute recurrent pancreatitis (ARP), chronic pancreatitis (CP), and chronic abdominal pain (CAP) is shown as reported in the original study. Each symbol represents a different study and the line indicates the median response rate. Endotherapy response is clearly greater in subjects with PD and ARP than in those with CP or CAP. Open triangles represent studies in which the definition of response to endotherapy includes at least one objective measure of pancreatitis. Solid triangles represent studies in which the definition of response to endotherapy requires no further treatment or intervention. Open circles represent studies in which the definition of response to endotherapy relies on patient perception of pain and/or therapy efficacy. Solid circles represent studies in which the definition of response to endotherapy is not well-defined.

75% of subjects. Response rates were lower in the other two groups, with an overall median response rate of approximately 30%–40% in patients with PD and CP or CAP. In total, nine studies have clearly differentiated between outcomes in patients with ARP, CP, and CAP. In all except one smaller study, which included only 18 patients [29], there was a clear increase in the response rate for patients with PD and ARP compared to those with CP and CAP [16,20,22,25,30,32,33]. One hypothesis for the low response rate of endotherapy in patients with PD and CP is that in these patients, the minor papilla duct may have undergone irreversible changes, preventing adequate ductal drainage despite endotherapy [37]. Additionally, pain perception in patients with PD and CP or CAP may be altered, contributing to a lower success rate [48]. Alternatively, PD may be merely an incidental finding in such patients and PD itself may not actually be related to CP or CAP.

A recent study by Bertin et al. [11] investigating the interaction between genetic mutations and anatomical abnormalities, such as PD, in the aetiology of ARP and CP suggested that PD may not be a sole cause of pancreatitis, but may rather act as a cofactor for predisposing genetic mutations. Bertin et al. [11] demonstrated that the rate of PD was similar in patients with idiopathic pancreatitis, alcoholic pancreatitis, and control patients. PD frequency was significantly increased in patients with certain genetic mutations, suggesting that PD may be a cofactor for pancreatitis in the context of other predisposing abnormalities [11]. To date, studies evaluating the interaction of factors that predispose individuals to pancreatitis are limited. Research in this area is currently ongoing through the North American Pancreatitis Study 2 (NAPS2) Consortium and is expected to shed light on the complex, multi-factorial aetiology of pancreatitis [7]. This ongoing work may help to explain why pancreatitis develops in only some patients with PD and to determine those in whom endotherapeutic treatment may be most beneficial.

The review presented here is limited by the fact that the majority of studies included were retrospective. In addition, the definition of clinical effectiveness of the endoscopic therapy varied among the studies. There is significant variability in patient response to endotherapy for the treatment of symptomatic PD, and it is clear that response to endotherapy is dependent on more than presentation. The level of ERCP expertise of the endoscopist could account for some of the variability, but this was not documented in most studies. However, as most studies were reported from tertiary referral centres, the level of endoscopist experience is expected to be high. Evaluation of endotherapy success is limited by the retrospective and often uncontrolled nature of studies in the literature. Additionally, there is significant heterogeneity between studies with respect to definition of endotherapy success and delineating groups with ARP, CP, and CAP. Finally, although a formal assessment of risk of bias was not performed, the vast majority of evidence regarding response to endotherapy in the literature is limited to case series, which are inherently prone to bias in selection of subjects, performance bias, attrition bias, detection bias, and reporting bias. However, the comprehensive nature of the review is a strength of our analysis, and publication bias was minimized by including both abstracts and full articles.

In conclusion, for patients with symptomatic PD, endotherapy is most likely to be effective at reducing the recurrence of pancreatitis

Table 4
Technical success and complications related to endotherapy.

Reference	Endotherapy	Technical success[a]	Acute		Chronic	
			Pancreatitis	Haemorrhage	Papillary restenosis	Clogged stent
Definition of response to endotherapy includes at least one objective measure of pancreatitis						
McCarthy et al. [36]	22	86%	5	0	0	10
Satterfield et al. [37]	10	ND	0	0	0	1
Lehman et al. [33]	52	ND	8	1	10	18
Chacko et al. [22]	48	86%	11	0	0	0
Lans et al. [34]	10	ND	0	0	0	0
Catalano et al. [19]	31	ND	3	–	3	–
Di Leo et al. [18]	20	70%	–	–	–	–
Kwan et al. [21]	21	ND	2	0	2	0
Ertan et al. [27]	25	ND	0	0	0	22
Jacob et al. [29]	18	17%	1	0	0	9
Definition of response to endotherapy includes no further treatment or intervention						
Vitale et al. [23]	24	ND	4	0	0	0
Attwell et al. [24]	184	ND	12	2	41	–
Definition of response to endotherapy relies on patient perception of pain and/or therapy efficacy						
Borak et al. [20]	113	ND	12	2	–	–
Gerke et al. [25]	53	ND	10	–	–	1
Heyries et al. [26]	24	ND	3	1	4	0
Boerma et al. [28]	16	ND	1	0	0	0
Kozarek et al. [30]	39	ND	8	0	3	4
Cohen et al. [31]	18	ND	6	0	0	0
Coleman et al. [32]	34	ND	20	1	0	2
Siegel et al. [35]	31	ND	31	0	0	17
Definition of response to endotherapy not well-defined						
Rustagi et al. [16]	33	ND	7	3	–	–
Yamamoto et al. [17]	12	ND	4	0	3	4
Total	838	85/117 (73%)	148/818 (18%)	10/734 (1%)	66/619 (11%)	88/457 (19%)

ND, not documented; –, not reported.
[a] Successful endotherapy procedure, regardless of patient outcome.

and pain in patients with ARP. Less than half of patients with PD and CP or CAP are likely to experience such a response to endotherapy. Patients with PD and CP or CAP may alternatively undergo celiac plexus block, intrathecal narcotic pump placement, bilateral thoracic splanchnicectomy, stone extraction, surgical sphincteroplasty, pancreatic tail resection, cystjejunostomy, or pancreaticojejunostomy. However, such interventions are also met with mixed success. Some have suggested that PD itself does not actually cause pancreatitis, but is rather associated with other risk factors, such as genetic mutations [49]. However, additional factors related to causes of CP or CAP and treatment success are unclear. Future studies of endotherapy outcomes that take into account genetic or other predisposing factors in addition to symptomology may allow for identification of the patients most likely to benefit from endotherapy. In addition, future studies should be careful to report the level of detail necessary for comparison to other studies of endotherapy for the treatment of PD, including definitions used to determine indication for procedure (ARP, CP, or CAP) and therapy success, success rate by indication, follow-up time, and the incidence of post-endotherapy complications. Of particular importance is consistency among success definitions. We propose use of quantitative measures appropriate to clinical presentation, such as those described by Chacko et al. [22]. For ARP, success should be defined as $\geq$50% reduction of acute pancreatitis episodes, hospitalization, or emergency department visits. For CP or CAP, success should be defined as $\geq$50% reduction in pain score on a visual analogue scale, use of narcotic analgesia, hospitalizations, or emergency department visits.

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Author contributions

All authors contributed to the conception and design; analysis and interpretation of the data; drafting of the article; critical revision of the article for important intellectual content; and final approval of the article.

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