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Treatment of disrupted and disconnected pancreatic duct in necrotizing pancreatitis: A systematic review and meta-analysis

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ABSTRACT

Background: Necrotizing pancreatitis may lead to loss of integrity of the pancreatic duct, resulting in leakage of pancreatic fluid. Pancreatic duct disruption or disconnection is associated with a prolonged disease course and particular complications. Since a standard treatment for this condition is currently lacking, we performed a systematic review of the literature to compare outcomes of various treatment strategies.

Methods: A systematic review was performed according to the PRISMA guidelines in the PubMed, EMBASE and Cochrane databases. Included were articles considering the treatment of patients with disrupted or disconnected pancreatic duct resulting from acute necrotizing pancreatitis.

Results: Overall, 21 observational cohort studies were included comprising a total of 583 relevant patients. The most frequently used treatment strategies included endoscopic transpapillary drainage, endoscopic transluminal drainage, surgical drainage or resection, or combined procedures. Pooled analysis showed success rates of 81% (95%-CI: 60–92%) for transpapillary and 92% (95%-CI: 77–98%) for transluminal drainage, 80% (95%-CI: 67–89%) for distal pancreatectomy and 84% (95%-CI: 73–91%) for cyst-jejunostomy. Success rates did not differ between surgical procedures (cyst-jejunostomy and distal pancreatectomy (risk ratio = 1.06, p = .26)) but distal pancreatectomy was associated with a higher incidence of endocrine pancreatic insufficiency (risk ratio = 3.06, p = .01). The success rate of conservative treatment is unknown.

Discussion: Different treatment strategies for pancreatic duct disruption and duct disconnection after necrotizing pancreatitis show high success rates but various sources of bias in the available studies are likely. High-quality prospective, studies, including unselected patients, are needed to establish the most effective treatment in specific subgroups of patients, including timing of treatment and long-term follow-up.

Introduction

Acute pancreatitis is one of the most common gastro-intestinal diseases requiring acute hospitalization [1,2]. Although most patients have a mild disease course, nearly 20% develops necrosis of the pancreas or peripancreatic tissue [3–6]. Necrosis of the pancreatic parenchyma may lead to loss of integrity of the

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pancreatic duct, consequently leading to duct disruption or disconnection [7]. This causes extraductal and extrapancreatic leakage of pancreatic fluids, which may result in several complications such as (recurrent) peripancreatic fluid collections with secondary infection, pancreatic ascites or, in case of leakage of pancreatic fluids towards other organs, pancreatic fistulas [8,9].

A disrupted duct is defined as a partial interruption of the duct integrity, whereas a disconnected duct is defined as a circumferential interruption of the pancreatic duct [10]. The treatment of this complication is not standardized, and includes conservative, medical, endoscopic, or surgical treatment. As there is no guideline available for this condition, treatment is currently at the judgement of the treating clinicians [11].

The aim of this systematic review is to identify different treatment options for pancreatic duct disruption and disconnection in patients with acute necrotizing pancreatitis, and to compare the outcomes of the different treatment strategies.

Methods

Study selection

The study was conducted according to the Systematic Reviews and Meta-Analysis (PRISMA) guidelines [12]. A systematic literature search was performed in the PubMed, EMBASE and Cochrane databases for studies published up to December 7th, 2017. Search terms were based on the disease ("pancreatitis") and the morphological/anatomical changes (e.g. disrupted or disconnected duct), with search field for the disease restricted to title and abstracts. Studies were restricted to English language. A detailed overview of the search and syntax is presented in the ***Appendix.***

Eligibility criteria

After removal of duplicates, studies were screened by title and abstract by two independent authors (SMvD, ER). Inclusion criteria were all studies considering acute necrotizing pancreatitis and disrupted or disconnected duct. Studies considering duct disruption as a result of chronic pancreatitis, or did not report on outcomes of these patients separately, were not included. Reviews, case reports, animal studies, editorials, opinion statements, studies with only patients under 18 years old, studies with fewer than 5 relevant patients and studies not describing visualization of the pancreatic duct anomalies were excluded. Of all remaining studies, full-text was assessed for eligibility. Final decision on eligibility was reached by consensus.

Critical appraisal

Methodological quality of the studies was independently assessed by two authors (SMvD, HCT), using the Newcastle-Ottawa Scale [13]. Using this grading system, one point is awarded for each segment if the study meets the criteria of the Newcastle-Ottawa Scale. For Comparability, two points could be assigned. The scoring algorithm indicates a poor quality study scoring up to 2 points, a fair quality study scoring 3–6 points and a good quality study scoring $\geq$7 points.

Data extraction

The following characteristics were extracted from all included studies: author, title, year of publication, country, type of study, number of patients in the study and number of relevant patients. All adult patients with a disconnection or disruption of the pancreatic duct as a result of acute pancreatitis were considered as relevant patients. Data concerning treatment of disconnected/disrupted duct syndrome were extracted separately. We extracted data on treatment strategies (including conservative treatment) and techniques and outcomes such as complications, mortality and re-interventions.

Statistical analysis

The procedural outcomes are reported success rates, with success being defined as resolution of the peripancreatic collection or pancreatic fistula-closure. Data from studies comparing two different treatments were pooled using meta-analysis software RefMan version 5.3 using a random-effects model. Outcomes of studies reporting only one procedure were pooled using a single-proportion meta-analysis STATA-module Metaprop in RStudio, version 3.4.3. Studies reporting on multiple modalities were not included in meta-analysis. Outcomes are presented as (pooled) proportion of success, risk ratio of success or standardized mean difference, all with 95% confidence intervals (CI). Statistical heterogeneity between the included studies was determined by forest plots and by calculating the I^2 index. A high I [2]-index represents a high suspicion of heterogeneity. In case of high hetereogeneity, sensitivity analysis was performed, exploring data using different effect models (both a random effect model and fixed effect model). All pooled event rates were shown in forest plots, regardless the level of heterogeneity.

Results

Search results

The search identified 2068 potentially relevant studies, 926 results returned from the EMBASE search, 1047 results from PubMed and 131 from the Cochrane database. After removing 819 duplicates 1249 studies remained. Based on screening the title and abstract, 1187 studies were excluded. After full-text assessment of the remaining 62 studies, 34 studies were additionally excluded: 8 reviews, 13 case-reports or series with fewer than 5 relevant patients, 4 editorials, 3 studies with a different cause of the duct disruption (e.g. chronic pancreatitis or trauma), 5 studies did not report the diagnosis of duct disruption or disconnection or a specific treatment. Furthermore, 2 studies were excluded because they reported on overlapping series [10,14–16]. For these studies we included the largest cohort [14,15]. Six studies only reported diagnosis and no therapy of duct anomalies [9,17–21]. Ultimately, 21 studies were included in this systematic review (Fig. 1) [7,14,15,22–39]. The total number of patients in the studies was 1181, of whom 583 were relevant for this review (i.e. patients with acute pancreatitis, and disconnected or disrupted pancreatic duct in whom outcomes were reported).

Study characteristics

All studies were observational cohort studies, published between 1991 and 2017 and originating from 7 different countries in 3 different continents. All but one study were retrospective cohort studies, three studies were designed as a retrospective analysis of a prospectively maintained database (Table 1). Randomized controlled trials are lacking. Reported treatments can roughly be divided in 3 types of interventions: (1) endoscopic transpapillary drainage procedures, (2) endoscopic transluminal drainage of pancreatic fluid collections and (3) surgical procedures (drainage and/or resection). Conservative treatment was not reported, although some studies reported that patients had conservative treatment before they underwent intervention (Tables 2–5). Six

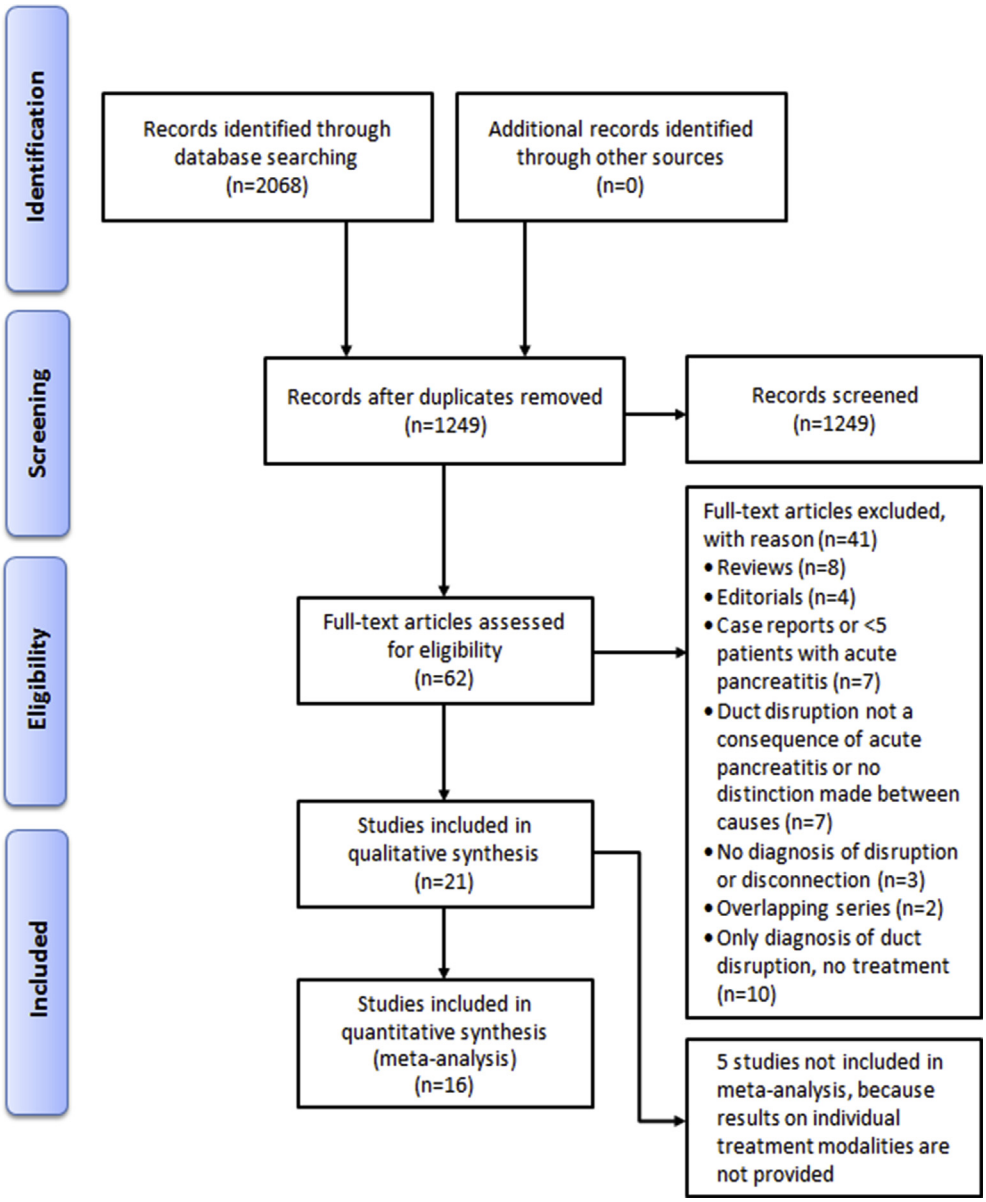

Fig. 1. Flow diagram.

studies report on the use of somatostatine analogs (e.g. octreotide), of which 2 reported it was not used, [34,39] and the other 4 studies reported percentages of patients that used it prior to intervention (34%, 92%, 50% and 33% respectively) [23,24,29,37].

In all but one studies, success was defined as a resolution of peripancreatic collections or fistula closure, one study did not mention how treatment success was defined [7]. In all studies duct disruption or disconnection was confirmed with one or more diagnostic modality. Twenty of 21 studies used ERCP and/or MRCP to diagnose this, whether or not in combination with another diagnostic modality. Details of the success definitions and diagnosis of the duct disruption per study are presented in Supplementary table 1.

Quality assessment

Quality assessment scores according to the Newcastle-Ottawa Scale are presented in Supplementary Table 2. One study scored as poor quality, [32] all other studies scored fair quality [7,14,15,22–31,33–39]

Endoscopic transpapillary drainage

Six studies reported on endoscopic transpapillary drainage for disrupted or disconnected duct [23,29,34,36,37,39]. Procedures vary from transpapillary placement of a nasopancreatic drain or a stent, either to bridge the disruption of the pancreatic duct, placing a stent only across the ampulla, or placing a drain through the duct disruption into the fluid collection. Success rates range from 48 to 100%. Meta-analysis showed a pooled success rate of 81% (95%-CI: 60–92%), with a $I^2 = 68\%$ (Fig. 2A). Differences within the studies in the presence of complete disconnection or partial disruption of the pancreatic duct are presented in Supplementary Table 3.

Endoscopic transluminal drainage

Four studies reported on endoscopic transluminal drainages as

Table 1
Study characteristics.

Author	Year of publication	Country	Inclusion period	Number of patients	Relevant patients[b]	Study design
Bang et al.	2016	USA	May 2014–Nov 2015	42	21	Prospective cohort study
Beck et al.	2011	USA	1993–2010	197	82	Cohort study, retrospective analysis of prospectively collected database
Das et al.	2016	USA	2008–2013	107	39	Retrospective cohort study
Devière et al.	1995	Belgium	Jun 1986–Jul 1993	13	9	Retrospective cohort study
Dhar et al.	2017	USA	2002–2014	42	42	Retrospective cohort study
Fischer et al.	2014	USA	July 2005–Jun 2011	50	43	Retrospective cohort study
Howard et al.	2001	USA	Jun 1995–Jun 2000	27	27	Cohort study[a]
Irani et al.	2012	USA	Oct 2002–Oct 2011	15	12	Cohort study, retrospective analysis of prospectively collected database
Jang et al.	2016	South Korea	2005–2013	84	32	Retrospective cohort study
Kozarek et al.	1991	USA	3 year period	18	10	Cohort study[a]
Lawrence et al.	2008	USA	Mar 1997–Jun 2003	189	30	Cohort study, retrospective analysis of prospectively collected database
Murage et al.	2010	USA	Nov 1995–Sept 2008	76	59	Retrospective cohort study
Pearson et al.	2011	USA	2002–2011	7	7	Retrospective cohort study
Pelaez-Luna et al.	2008	USA	Jan 1999–Jul 2006	31	31	Retrospective cohort study
Rana et al.	2010	India	"last 12 years"	23	15	Cohort study[a]
Rana et al.	2015	India	"last 4 years"	35	35	Retrospective cohort study
Sharaiha et al.	2016	USA	Jan 2014–May 2015	124	19	Retrospective cohort study
Smoczynski et al.	2015	Poland	2001–2013	22	22	Retrospective cohort study
Telford et al.	2002	USA	1993–2001	43	24	Retrospective cohort study
Téllez-Aviña et al.	2016	Mexico	2008–2015	21	18	Cohort study, retrospective analysis of prospectively collected database
Yokoi et al.	2016	Japan	Jan 2005–Feb 2014	15	6	Retrospective cohort study

[a] Unclear if prospective or retrospective study design.
[b] Patients with disrupted or disconnected pancreatic duct as a result of acute pancreatitis.

treatment of duct disruption [15,22,24,38]. All studies used plastic stents for transgastric or transduodenal drainage of the fluid collection caused by the duct disruption. Time from the start of the disease until intervention was not reported. Three out of four studies reported to use plastic pigtail stents, which were left indefinitely or 'long-term' [15,22,38]. One study did not report specifications on the type of drain or stent [24]. Success rates range from 81 to 100%. Meta-analysis showed a pooled success rate of 92% [95%-CI: 77–98%] with a $I^2 = 32\%$ (Fig. 2B).

Surgical treatment

Six studies reported on surgical procedures [7,14,25,26,31,32]. The procedures described are either distal pancreatectomy or a Roux-and-Y internal drainage of the cyst or fistula tract. The choice of procedure was at the discretion of the surgeon in all studies. Meta-analysis of the success rates of the two procedures showed a pooled success rate of 80% [95%-CI: 67–89%] for distal pancreatectomy and 84% [95%-CI: 73–91%] for Roux-and-Y internal drainage (Fig. 2C and D). There were no differences (risk ratio = 1.06, p = .26) between both strategies. Distal pancreatectomy was associated with more intraoperative blood loss (std. mean difference = 2.30, p = .02) and a higher incidence of pancreatic endocrine insufficiency (risk ratio = 3.06, p = .01). No differences were found regarding exocrine insufficiency (risk ratio = 1.17, p = .68) (supplementary figures).

Other

Five studies reported on different procedures than described above, or combined treatments [27,28,30,33,35]. All procedures and related success rates and complications are reported in Table 5. Due to the heterogeneity of treatment a meta-analysis was deemed not possible.

Discussion

Disruption or disconnection of the pancreatic duct is a severe complication of necrotizing pancreatitis for which no standardized treatment is defined. Which treatment is currently chosen is based on the discretion of the treating clinician and not on evidence-based guidelines. This study is the first systematic review reporting on the potential merits and outcomes of the various treatment strategies available for disrupted or disconnected pancreatic duct syndrome including conservative treatment, endoscopic transpapillary drainage, endoscopic transluminal drainage, surgical drainage, distal pancreatectomy, and combinations of the aforementioned procedures. The pooled success rates of these treatment strategies are all high, over >80%. The success rate of conservative treatment, however, remains unknown.

In all studies the disconnection or disruption of the pancreatic duct was radiologically proven. However, it was not always clear if the reported treatment was the initial treatment performed in the analyzed patients. It cannot be ruled out that some patients had already undergone other types of treatment that failed. This may have introduced bias. There was a great variability in the timing of the different interventions within and between studies. Endoscopic procedures were usually performed in a relatively early stage of the disease and the surgical procedures later in the course of pancreatitis, i.e. up to several months after the onset of the disease,

Table 2
Endoscopic treatment – Transpapillary procedures.

Study	Year	Included patients	Relevant patients	Intervention	Prior therapy for duct disruption/ disconnection	Time until intervention (days)	Succes rate	Time until succes	Procedure-related Complication	Follow-up (median)
Das et al.	2016	107[a]	39	35 endoscopic transpapillary drainage with transpapillary stent[b] - Sphincterotomy, pancreatic duct stone extraction and -duct stricture dilatation was based upon discretion of endoscopist	Conservative management (including percutaneous drainage and pancreatic rest, not specified for acute pancreatitis patients)	Mean 33 days from diagnosis of duct disruption	24/35	NR	Not specified for subgroup of acute pancreatitis patients	Overall 21 months (range 1–84)
Kozarek et al.	1991	18	10	Transpapillary stent (n = 9) and/or transpapillary drain (n = 4)	7/10 had previous percutaneous or surgical pancreatic drainage	Median 6 weeks (range 1–18 months)	9/10 resolution of fluid collection 9/10 resolution of symptoms	6 weeks	Infection (n = 1); Stent occlusion (n = 1). 3 patients required subsequent surgery: tail resection (n = 2); Head resection (n = 1)	Median 16 months (range 3–36 months)
Rana et al.	2010	23	17	Transpapillary nasopancreatic drain - Bridging of the disruption (n = 15) - As near as possible to the disruption (n = 6) - Unsuccessful (n = 2)	Percutaneous drainage	NR (At least 6 weeks after prior percutaneous drainage)	Bridging: no recurrence of external fistula Not-bridging: 2 successful	mean 5.37 (range 2–8) weeks	1 stent occlusion Long term complications: Bridging: 1 pseudocyst Non-bridging: 1 pseudocyst 1 bleeding pseudoaneurysm	Mean 38 (range 2–102 months)
Smoczynski et al.	2015	22	22	First active drainage: - Transpapilary nasopancreatic drain - In the walled-off necrosis (n = 18) - Bridging the disruption (n = 4) After active drainage: transpapillary stent in pancreatic duct. - Proximal to the PD leak (n = 10) - Bridging the PD leak (n = 12)	None	Mean 16 (range 5–50), weeks	Therapeutic success in 20/22 patients. 2/22 patients clinical symptoms of WOPN disappeared, but the size of the collection remained >3 cm	NR	3/22 gastrointestinal bleeding, conservatively treated At 1 year follow up: 4/22 recurrent fluid collection (all with disconnected duct); 2 treated with transluminal drainage, 2 surgically treated	1 year
Telford et al.	2002	43	24	41 Transpapillary stent placement - Short stent (n = 16) - Into the disruption (n = 13) - Bridging the disruption (n = 14) 2 nasopancreatic drain	24/43 total parenteral nutrition and somatostatin analogue; 16/43 percu-taneous drain; 1 endoscopic cystduodenostomy; 5 surgical cyst drainage or pancreatic debridement	NR	Resolution of PD disruption in 25/43 patients. AP patients: Successful 11, 12 unsuccessful	NR	4/43 clinical deterioration	Median 24 months
Yokoi et al.	2016	15	6	Transpapillary bridging stent (n = 3) If bridging not possible:	Standard treatment for acute pancreatitis, including step-up approach for infected necrotizing pancreatitis:	Median 16.5 days (range 1–300 days)[c]	All successful fistula closure	Median time to fistula closure after transpapillary treatment 45	No procedure related complications. 2 patients eventually	NR

(*continued on next page*)

Table 2 (*continued*)

Study	Year	Included patients	Relevant patients	Intervention	Prior therapy for duct disruption/ disconnection	Time until intervention (days)	Succes rate	Time until succes	Procedure-related Complication	Follow-up (median)
				Transpapillary drain into collection (n = 3)	All patients had one or more percutaneous drain(s)			(16–330) days.[c]	died of infectious complications	

NR = not reported.
[a] *Patients with necrotizing pancreatitis were excluded from this study*.
[b] 5/35 patients underwent concurrent transluminal drainage for large peripancreatic fluid collections.
[c] Not specified for only patients with duct disruption.

Table 3
Endoscopic treatment – (mainly)Transluminal drainages/cysto-ostomies.

Study	Year	Included patients	Relevant patients	Intervention	Prior therapy for duct disruption/ disconnection	Time until intervention (days)	Succes rate	Time until succes	Procedure-related Complication	Follow-up (median)
Bang et al.	2016	42	21	Endoscopic ultrasound-guided transluminal drainage, with plastic stents indefinitely left in situ	NR	NR	20/21 no recurrence	8 weeks	–	272 days (range 68–501)
Devière et al.	1995	13	9	(1 transpapillary drainage), 3 cystogastrostomy[a], 2 cystoduodenostomy[a], 2 combined procedures (1 surgical pancreatojejunostomy)	-Total parenteral nutrition and somatostatin –4 previous drainage attempts	NR	Long term: 8/8 endoscopically treated 0/1 surgically treated	4–8 weeks	1 infected pseudocyst. Furthermore uncomplicated	mean 30.6 months (range 12–72)
Rana et al.	2015	35	35	Transluminal drainage with stents left in place long term	NR	NR	All successful resolution of walled-off necrosis	NR	Spontaneous stent-migration in 8/35 patients, causing recurrent fluid collection in 3 patients.	Mean 28.2 (±14.0) months, range 6–50
Téllez-Aviña et al.	2016	21	18	Endoscopic transluminal drainage with plastic pigtail stents	NR	NR	Clinical success in 17/21 (80.9%) patients 3 required repeat endoscopy 1 required surgery	NR	1 post-ERC P pancreatitis. 2 (9%) prosthesis migrations; 1(4.7%) infection after drainage, 1 (4.7%) prosthesis migration with suspicion of perforation not confirmed by surgery and 1 (4.7%) patient who developed an infection after prosthesis migration. Diabetes mellitus n = 11	Median 28 (range 7–76) months

NR = Not Reported.
[a] Transluminal drainage with sphincterotomy (n = 3), transluminal drainage without sphincterotomy (n = 2).

probably after failed conservative or failed endoscopic treatment. This brings into question how reliable the reported success rates are in relation to timing and preceding treatments and whether the success of a treatment can be predicted. This, however, cannot be answered with the current data. Because of the high hetereogeneity in the included studies, we used a random effects model for our meta-analysis. We performed a sensitivity analysis, using different models, showing that results remain similar (success rates did not differ >10% between different analysis, data not shown). Because of the heterogeneity, and the fact that the majority of studies only included small numbers of patients, results should be interpreted with caution. A high risk of publication bias remains.

Partly due to uncertainties about the indication and timing of the reported treatments, a scientifically sound and valid comparison between different treatments cannot be made. Confounding by indication likely occurred. For instance, an attempt to endoscopically bridge the pancreatic duct defect will not always be possible and may end up in doing a different procedure such as a the placement of a non-bridging stent [23,29,34,36,37,39]. Having a complete disruption (i.e. disconnection) makes placing a bridging stent almost impossible. Therefore certain conditions influence the likelihood of success and thereby the outcome of a specific procedure. Otherwise, in studies on surgical procedures, the treatment of choice is often decided during operation, based on peroperative findings, and the preference and skill of the surgeon [7,14,25,26,31].

The long-term success of each treatment strategy also remains unclear. Because of this and the aforementioned issues it cannot be concluded form the current data which treatment is superior. A suggestion would be to introduce a ‘step-up’ treatment algorithm, starting with conservative treatment, gradually progressing from minimally-invasive to more invasive surgical procedures. These step-up approaches have already successfully been practiced in other pancreatic conditions [40–44]. Although distal pancreatectomy is associated with a high success rate, it has the highest risk of long-term endocrine and exocrine insufficiency. Conversely, with the current evolution of advanced endoscopy, it can be questioned whether there will still be a prominent role for surgery in the treatment of this condition. Surgical cyst-jejunostomy, for example, has essentially been replaced by transluminal cyst-gastrostomy [45,46]. However, rigorous surgery may provide a definite

Table 4
Surgical procedures.

Study	Year	Included patients	Relevant patients	Intervention	Prior therapy for duct disruption/ disconnection	Time until intervention (days)	Succes rate	Time until succes	Procedure-related Complication	Follow-up (median)
Beck et al.	2011	197	82	42 surgery: ● 30 Roux-en-Y drainage, dependent on anatomy → 19x jejunum to walled-off necrosis → 2x jejunum to drain traject → 9x jejunum on pancreatic duct ● 12 resection pancreatic remnant	10/82 patients had percutaneous drainage, unsuccessful	>8 weeks Mean time until operation = 3.2 ± 0.8 months	Overall success rate surgery = 96% Patients without intervention NR	8 weeks	1% mortality Persistent fever and leukocytosis in 13/19 patients with Roux-en-Y jejunum to WOPN	47 months
Dhar et al.	2017	42	42	21 fistulojejunostomy 21 distal pancreatectomy	None	NR	17/21 Fistulojejunostomy 20/21 distal pancreatectomy	NR	Significantly more blood loss ($p < .01$)and blood transfusion in DP ($p < .01$); worsening of endocrine insufficiency in 52.4% vs 19.1% in FJ-group($p = .02$)	12 months (range 3–69 months)
Fischer et al.	2014	50	43	cDPSD Necrosectomy with tail resection (n = 28)[a] dDPSD: Distal pancreatectomy with splenectomy(n = 15)[b]	Endoscopic procedures: cDPSD (n = 10) dDPSD (n = 15) Percutaneous procedure cDPSD (n = 9) dDPSD (n = 3)	cDPSD: median(range): 60 (26–4793) dDPSD: median(range): 440 (69–5235)	25% recurrent pseudocyst	NR	cDPDS: 10(36%) Clavien Dindo class II, 0 Class III, 2(8%) Class IVa; 10(36%) exocrine and 16(57%) endocrine insufficiency dDPDS: 4(27%) Clavien-Dindo Class II; 0 Class III, 0 Class IV; 9 (60%) exocrine and 11(73%) endocrine insufficiency	Mean 17.6 months
Howard et al.	2001	27	27	Roux-en-Y internal drainage (n = 13) - 9 pancreaticojejunostomy - 4 cystojejunostomy Distal pancreatectomy-splenectomy (n = 14)	Prior surgery, unspecified, in 8 patients in the roux-en-y-group, 7 in de distal pancreactectomy group	6.1 (±2.3) vs 4.9(±2.0) months	Roux-en-Y 100% Distal pancreatectomy 93%	NR	Death 1(8%) vs 1(7%); Bleeding 1(8%) vs 1(8%); Wound infection 2(15%) vs 0(0%); Postoperative Diabetes 2(15%) vs 0(0%); wound infection 2(15%) vs 0(0%); pneumonia 1(8%) vs 0(0%); Significant more intraoperative blood loss in distal pancreatectomy ($P < .0001$)	Median 17 (±8) vs 18 (±9) months
Murage et al.	2010	76	59	Distal pancreatectomy (n = 42) Roux-en-Y internal drainage (n = 34) - Pancreatojejunostomy (n = 18) - Cystojejunostomy (n = 10) - Fistulojejunostomy (n = 6)	55% pancreatic debridement and external drainage		DP: 74% success rate: 11(26%) symptomatic recurrences; ID 82% success rate: 6(18%) symptomatic recurrence	NR	More intraoperative blood-loss in DP ($P = .001$); no differences in major perioperative morbidity rates (≥IIIa; 14% vs 6%; $P = .103$), 90-day mortality rates (0 vs 0; $P \geq .05$), or in-hospital duration of stay (11 days vs 9 days; $P = .080$), DM (12% vs 3% $p = .063$) or steatorrhea ($p = .408$ between DP vs ID	Median 22 months
Pearson et al.	2011	7	7	Roux-en-Y internal drainage	Conservative medical treatment or endoscopic intervention, not specified	Median 270 days (range 164–365)	100% successful resolution, no recurrences during follow-up	NR	1 delayed bleeding of splenic artery requiring distal pancreatectomy and splenectomy	Median 264 days (range 29–740)

NR = Not reported.
[a] CDPSD = Concurrent diagnosis of DPSD with AP.
[b] DDPSD = Delayed diagnosis of DPSD.

solution for patients, withholding them from the burden of multiple less invasive procedures and prolonged morbidity, as seen in chronic pancreatitis patients [42,47,48].

Conservative management, usually, is the first step of treatment. Some clinicians nowadays actively search for the presence of duct disruptions in necrotizing pancreatitis, in order to start treatment in a relative early phase of the disease. It is unclear, however, which patient category will benefit from conservative treatment and therefore a too active approach may cause overtreatment. On the other hand, early diagnosis and treatment may reduce the delay in treatment, which may be beneficial in patients who often already suffered from a prolonged disease course.

Table 5
Other/combined procedures.

Study	Year	Included patients	Relevant patients	Intervention	Prior therapy for duct disruption/ disconnection	Time until intervention (days)	Succes rate	Time until succes	Procedure-related Complication	Follow-up (median)
Irani et al.	2012	15	12	Outside-in interventional radiologist−guided transgastric/-duodenal puncture (n = 10); Inside-out endoscopic ultrasound-guided fistula puncture (n = 3); Reconnecting the disconnected duct: Interventional radiologist−guided transpapillary access and internalization (n = 2)	NR	NR	100%, no recurrences	Median 7 days (range 1−73 days	No mortality; Adverse events in 4/15(27%): 1 fever requiring oral antibiotics, 5 new PFC (2 asymptomatic): 4 spontaneous migration of transluminal stents, of which 3 developed a new symptomatic PFC.	Median 25 months (range 6−113)
Jang et al.	2016	84	32	Disconnection: percutaneous drain (n = 10); Endoscopic ultrasound-guided transluminal drain(n = 5); Attempted transpapillary drainage (n = 5, successful in 1); Endoscopic necrosectomy (n = 5); surgical resection (n = 2) Partial disruption: attempted transpapillary drainage (n = 12, successful in 11); Endoscopic ultrasound-guided transluminal drainage (n = 6); Endoscopic necrosectomy (n = 3); Percutaneous drain (n = 2)	NR	Median 39 days (range 21−178 days)	Disconnection: 29%, not specified per treatment Partial disruption: 67%, not specified per treatment	NR	NR	Median 512 days (35 −3500)
Lawrence et al.	2008	189	30	Transluminal drain (n = 15); Transpapillary drain (n = 7); surgical drainage(cystenterostomy or cystgastrostomy) (n = 5); percutaneous drain (n = 2).	NR	NR	Initial success/recurrence rate (rec):Transluminal drain 11/15 (73%), rec 5/11(45%); transpapillary drain 5/7 (71%), rec 2/5(40%); surgical drainage 5/5 (100%), rec 3/5(60%); percutaneous drain 1/2 (50%), rec 1/1 (100%)	NR	1 mild post-sphincterotomy bleeding.	Median 38 months (range 3−94)
Pelaez-Luna et al.	2008	31	31	Endoscopic treatment (n = 26) - Transgastric (n = 12) - Transduodenal (n = 10) - Transpapillary (n = 4) Surgical treatment (n = 12) (Primary surgery (n = 5); After endoscopic treatment (n = 7)) - Cystenterostomy (n = 3) - Distal pancreatectomy (n = 5) - Necrosectomy, debridement end/or external drainage (n = 2) - Necrosectomy, followed by pancreatectomy in second surgery (n = 1) - Necrosectomy followed by external cyst drainage (n = 1)	NR	Median 56 (range 3 −251) days between initial AP event and diagnosis of DPDS. Time to first intervention not reported	Endoscopic improvement: 19 (61%); Pancreatic-duct integrity reestablished 3/19; Endoscopic failure that required surgery 7 (23%)	NR	Deaths 0%; CP/pancreas atrophy 8 (26%); Chronic abdominal pain 1 (3%); Persistent pancreatic fistula (duodena, gastric, cutaneous) 1(3%); Complete resolution 3 (10%) Persistent but smaller collections 13 (42%); DM 5 (16%); Lost immediately after last intervention 8 (26%)	Median 6.5 (range 0.5 −90) months
Sharaiha al.	2016	124	19	Transluminal (lumen-apposing metal) stent with concurrent ERCP with pancreatic stenting	None	NR (At least 4–6 weeks after onset of pancreatitis)	Not specified for patients with duct disconnection/disruption	Not specified for patients with duct disconnection/ disruption	Not specified for patients with duct disconnection/disruption	Not specified for patients with duct disconnection/ disruption

NR = Not reported.

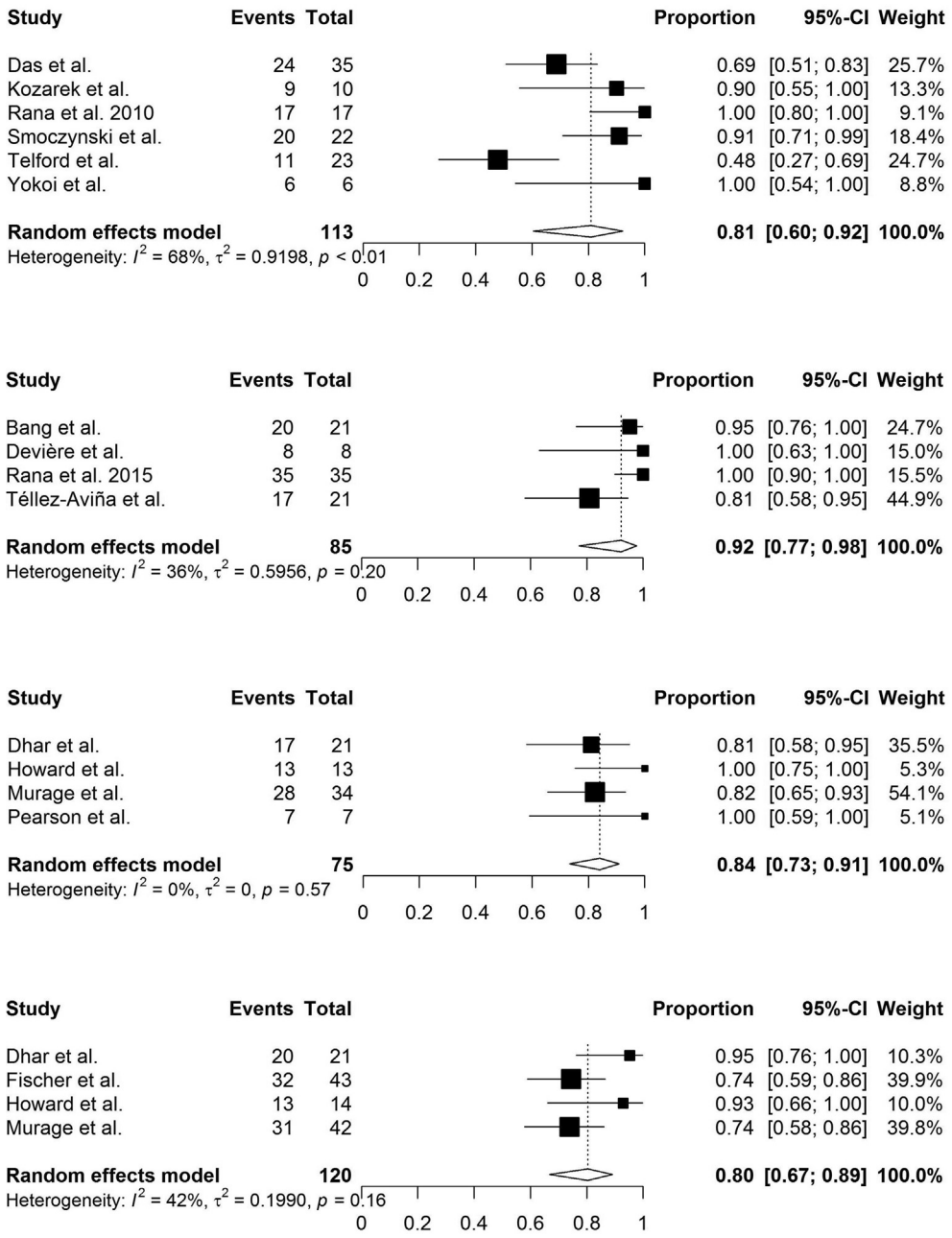

Fig. 2. **A** – Pooled success rate of endoscopic transpapillary drainage. **B** - Pooled success rate of endoscopic transluminal drainage. **C** – Pooled success rate of Roux-en-Y internal drainage. **D** – Pooled success rate of distal pancreatectomy.

This study has some limitations. First, data on the conservative and medical treatment of disconnected/disrupted duct are lacking. This is relevant since probably not all patients require endoscopic or surgical treatment. Second, the majority of included studies are retrospective by design and only present results of a single treatment strategy, while in all probability some patients may have already failed preceding treatments. Moreover, retrospective identification of patients might have introduced selection bias, since patients with the target condition not receiving a diagnostic ERCP or MRCP could not be identified. There is no systematic diagnostic work-up to identify duct disruption, possibly leaving many patients with a duct disruption out of the study cohorts, again, not reporting the conservatively treated patients. Third, most studies lack a comparator making it impossible to analyze the potential superiority of a particular treatment.

A strength of this study is that it is the first systematic review on this subject, and that we were able to perform a meta-analysis of the success rates of the different treatments. Since many of the treatment decisions are based on the site and extent of morphological changes due to necrosis, this systematic review has focused on the studies in which a duct anomaly was proven. Previous studies focused on the treatment of only the complications of disconnected pancreatic duct syndrome (e.g. pseudocysts and pancreatocutaneous fistula), [49] without paying attention to the anatomical substrate as the cause of this complication. The strength of this review is our focus on the cause of the complications: the disruption or disconnection of the pancreatic duct. This duct anomaly instantly provides the possibilities for the different

treatment strategies.

In conclusion, this study provides an overview of the treatment options for patients with a disruption or disconnection of the pancreatic duct after acute necrotizing pancreatitis. The current literature lacks in quality with only one prospective cohort study available and no randomized controlled studies. It is therefore inconclusive about the best treatment of choice. Indication for invasive procedures in the treatment of disrupted and disconnect pancreatic duct remains unclear, due to the lack of a systematic diagnostic work-up, the lack of risk analysis to predict the treatment outcome of the various treatment modalities and the absence of studies reporting on conservative treatment. Future research should address the indication, timing and long-term success of all different treatment strategies in order to devise an evidence-based treatment algorithm.

Disclosure

There are no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2019.08.006.

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