

# Endoscopy

## Impact of long-term transmural plastic stents on recurrence after endoscopic treatment of walled-off pancreatic necrosis

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### Abstract:

Background and study aims:

Endoscopic transmural drainage (ETD) using double pigtail stents (DPS) is a well-established treatment for walled-off pancreatic necrosis (WON). This study aimed to compare outcomes in patients undergoing ETD with DPS left indwelling versus those where stents were removed or migrated.

Patients and methods:

This retrospective, multicenter cohort study included patients with WON who underwent ETD using DPS between July 2001 and December 2019. The primary outcome was recurrence of a pancreatic fluid collection (PFC). Secondary outcomes were long term complications and recurrence-associated factors. Competing risk regression analysis considered DPS removal or migration as time-varying covariate.

Results:

Among 320 patients (median age 58, 36% female), DPS were removed in 153 (47.8%), migrated spontaneously in 27 (8.4%), and remained indwelling in 140 (43.8%). PFC recurrence was observed in 57 patients (17.8%): after removal in 39 (25.5%), after migration in 4 (14.8%) and in patients with indwelling DPS in 14 patients (10%). In 25 patients (7.8%) drainage of recurrent PFC was indicated. Risk factors for recurrence were DPS removal or migration (HR: 3.45, 95%CI: 1.37–8.70) and presence of a disconnected pancreatic duct (HR: 3.45, 95%CI: 1.84–14.0).

Conclusions:

Among patients who undergo ETD of WON, leaving DPS in situ seems to lower the risk on recurrent fluid collections, without any long term DPS-related complications. These results suggest that DPS should not be routinely removed and can be safely left indwelling indefinitely.

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1 **Impact of long-term transmural plastic stents on recurrence after**  
2 **endoscopic treatment of walled-off pancreatic necrosis**

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1 **ABSTRACT**

2 *Background and study aims:*

3 Endoscopic transmural drainage (ETD) using double pigtail stents (DPS) is a well-established treatment  
4 for walled-off pancreatic necrosis (WON). This study aimed to compare outcomes in patients undergoing  
5 ETD with DPS left indwelling versus those where stents were removed or migrated.

6

7 *Patients and methods:*

8 This retrospective, multicenter cohort study included patients with WON who underwent ETD using DPS  
9 between July 2001 and December 2019. The primary outcome was recurrence of a pancreatic fluid  
10 collection (PFC). Secondary outcomes were long term complications and recurrence-associated factors.  
11 Competing risk regression analysis considered DPS removal or migration as time-varying covariate.

12

13 *Results:*

14 Among 320 patients (median age 58, 36% female), DPS were removed in 153 (47.8%), migrated  
15 spontaneously in 27 (8.4%), and remained indwelling in 140 (43.8%). PFC recurrence was observed in 57  
16 patients (17.8%): after removal in 39 (25.5%), after migration in 4 (14.8%) and in patients with indwelling  
17 DPS in 14 patients (10%). In 25 patients (7.8%) drainage of recurrent PFC was indicated. Risk factors for  
18 recurrence were DPS removal or migration (HR: 3.45, 95%CI: 1.37–8.70) and presence of a  
19 disconnected pancreatic duct (HR: 3.45, 95%CI: 1.84–14.0).

20

21 *Conclusions:*

22 Among patients who undergo ETD of WON, leaving DPS in situ seems to lower the risk on recurrent fluid  
23 collections, without any long term DPS-related complications. These results suggest that DPS should not  
24 be routinely removed and can be safely left indwelling indefinitely.

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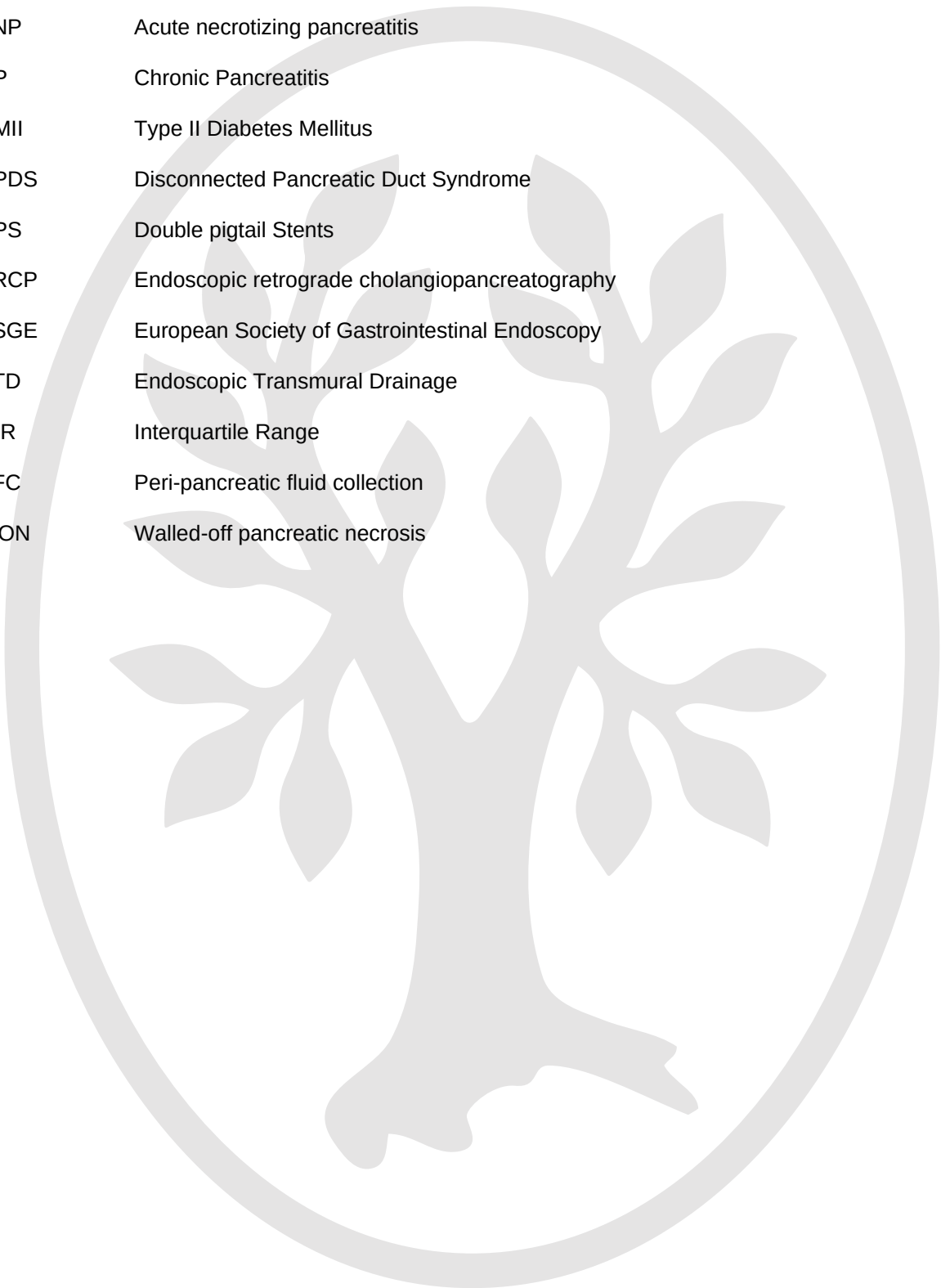
1 **ABBREVIATIONS**

|    |      |  |
|----|------|--|
| 2  | ANP  | Acute necrotizing pancreatitis                 |
| 3  | CP   | Chronic Pancreatitis                           |
| 4  | DMII | Type II Diabetes Mellitus                      |
| 5  | DPDS | Disconnected Pancreatic Duct Syndrome          |
| 6  | DPS  | Double pigtail Stents                          |
| 7  | ERCP | Endoscopic retrograde cholangiopancreatography |
| 8  | ESGE | European Society of Gastrointestinal Endoscopy |
| 9  | ETD  | Endoscopic Transmural Drainage                 |
| 10 | IQR  | Interquartile Range                            |
| 11 | PFC  | Peri-pancreatic fluid collection               |
| 12 | WON  | Walled-off pancreatic necrosis                 |

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## 1 Introduction

2 Acute pancreatitis can result in walled-off pancreatic necrosis (WON) in about 20% of patients [1].

3 Invasive intervention can be indicated for patients with acute necrotizing pancreatitis (ANP) and clinically

4 suspected or proven infected necrosis, in line with the European Society of Gastrointestinal Endoscopy

5 (ESGE) guideline recommendations [2]. Other indications of invasive treatment may be organ

6 compression or abdominal compartment syndrome. Infected pancreatic necrosis is a serious condition

7 associated with a prolonged and severe disease course, with mortality rates reported to be as high as

8 40% [3]. Furthermore, the loss of viable pancreatic parenchyma can cause disruption or disconnection of

9 the pancreatic duct, resulting in disconnected pancreatic duct syndrome (DPDS) [4]. This condition can

10 lead to ongoing formation of peri-pancreatic fluid collections (PFCs) and pancreatic fistula [5].

11 The ESGE recommends a step-up approach for the treatment of ANP, with percutaneous or

12 endoscopic transmural drainage (ETD) as a first step, followed by necrosectomy if necessary [2]. If

13 technically feasible the endoscopic approach is preferred [6, 7]. Prospective comparative studies show no

14 differences in short term outcome between either placement of double-pigtail stents (DPS) or lumen

15 apposing metal stents (LAMS) [8-10]. However, the guidelines do not provide a recommendation on the

16 duration of DPS to remain in situ in for both patients with and for those without DPDS. Studies have

17 shown varying rates (0-38%) of PFC recurrence and complications associated with DPS removal or

18 leaving DPS indwelling [2, 11-14].

19 Our current study aims to investigate the rate of PFC recurrence in patients undergoing ETD for

20 treatment of WON using DPS, both for patients in whom these were removed electively or migrated

21 spontaneously, and in patients in whom these were left long-term indwelling. In addition, possible risk

22 factors associated with recurrence of PFC are evaluated.

23

24

## 1 **Material and methods**

### 2 **Study design and patient selection**

3 A multicenter, retrospective cohort study was conducted at three Dutch tertiary referral centers for  
4 pancreaticobiliary diseases, on patients who underwent ETD for the treatment of WON between July  
5 2001 and December 2019. The patients were identified from the local endoscopy database (Endobase or  
6 Clinical Assistant), in which all endoscopic procedures and reports are prospectively registered. WON  
7 was defined according to the revised Atlanta guidelines 2018 as a mature, encapsulated collection of  
8 pancreatic and/or peri-pancreatic necrosis that has developed a well-defined inflammatory wall [2]. As  
9 terminology of PFCs has changed over time, we retrospectively checked these criteria for all patients in  
10 consultation with an experienced gastroenterologist and radiologist experienced in hepatico-pancreato-  
11 biliary imaging, for all diagnostic imaging studies that were performed. Patients with ETD for cysts other  
12 than WON, such as pseudocysts, were excluded from this study. Initial drainage by LAMS was not an  
13 exclusion criteria, as long as DPS were placed after LAMS removal. This study was conducted in  
14 accordance to the guidelines of the Helsinki Declaration and was approved by the ethics committee of all  
15 participating centers (MEC-2019-0116).

16

### 17 **Intervention**

18 Initially, ETD was performed, with step-up endoscopic necrosectomy if clinically indicated. Endoscopic  
19 Ultrasound (EUS) was performed to visualize the WON, and the gastric or duodenal wall was punctured  
20 to create a fistulous tract using a cystotome or balloon dilatation. Subsequently DPS were placed under  
21 fluoroscopic guidance. The number, length, and diameter of the DPS were left to the discretion of the  
22 treating physician. If the WON contained a significant amount of solid necrotic tissue, a nasocystic  
23 catheter was routinely placed to irrigate and stimulate liquefaction of necrosis. Necrosectomy was  
24 performed during the first ETD if indicated or after the initial ETD, depending on whether the patient  
25 improved clinically or whether an infection of the WON was diagnosed. During a necrosectomy the  
26 fistulous tract was dilated to allow for endoscope access with a therapeutic gastroscope and necrotic  
27 tissue was removed.

28



## 1 **Data collection**

2 Using electronic patient records, data were collected on demographic factors (i.e. sex and age), medical  
3 history, etiology of the pancreatitis, size of WON, number of DPS placed, and number of endoscopic,  
4 radiological or surgical interventions for treatment of WON. WON size was measured using length, width  
5 and height. Length was defined as the longest length in the axial plane in centimeters (cm). In the same  
6 axial plane, the longest width (in cm) was measured perpendicular on the longest length. In addition, in  
7 the frontal plane the longest height (in cm) was measured.

8 In addition, long term complications, including chronic pancreatitis (CP), exocrine and/or exocrine  
9 insufficiency or type II Diabetes Mellitus (DMII), pancreatic fistula, or chronic pancreatic pain syndrome  
10 (>30 days after DPS placement) were recorded. Complications related to DPS, such as migration and/or  
11 perforation, were also recorded. Time to migration was based on the date of imaging confirming  
12 migration. Finally, the number of patients diagnosed with DPDS was recorded. For all patients, the  
13 maximum follow-up time was based on data availability in individual medical records; i.e. last moment of  
14 outpatient contact or death.

15

## 16 **Cross-sectional imaging during follow up**

17 After endoscopic treatment of WON, cross-sectional imaging was not routinely performed in every patient.  
18 Follow up imaging after endoscopic treatment of WON was performed in case of suspicion of PFC related  
19 symptoms or for diagnostic reasons other than detection of PFCs (for example, CAT scan for pseudo-  
20 aneurysm). When cross-sectional imaging or upper gastrointestinal endoscopy was performed during  
21 follow-up, this provided additional information on the status of DPS; i.e. whether they were still left  
22 indwelling or had migrated.

23

## 24 **Study outcomes**

25 The study's primary endpoint was the recurrence of PFC. As imaging to confirm WON resolution was not  
26 routinely performed, time to recurrence was calculated as time from last intervention to date of recurrence  
27 of PFC. Recurrence was defined as a PFC on imaging studies after initial successful treatment of WON,

1

1 and further classified as a true recurrent PFC in case of detection at the initial site of endoscopic  
2 drainage, or a new PFC in case of detection not at the initial site of endoscopic drainage.

3

4 The secondary endpoints were factors associated with PFC recurrence. Presence of DPDS was  
5 diagnosed at magnetic resonance cholangio-pancreatography, computed tomography (CT) scan or  
6 ERCP, and defined as a complete or incomplete disruption of the pancreatic duct as judged by an  
7 experienced radiologist in HPB imaging.

8

### 9 **Statistical analysis**

10 The statistical analysis included descriptive statistics using mean and standard deviation for normally  
11 distributed variables, and median and interquartile range (IQR) for non-normally distributed continuous  
12 variables. Categorical and dichotomous variables were described using frequencies and proportions (%).  
13 Competing risk analysis, using cause-specific hazard regression, was performed to assess the  
14 association between several variables and PFC recurrence. In addition, a sensitivity analysis for  
15 symptomatic PFC recurrence was performed. Variables included in these analyses were based on current  
16 literature or expert opinion. Variables included in multivariable regression were based on the statistical  
17 significance of the regression coefficients in the univariate model. In line with cause-specific hazard  
18 regression, all patients who died without a recurrence of PFC were treated as censored. DPS removal or  
19 migration of all DPS was treated as a combined time-varying covariate. Whenever migration of DPS  
20 occurred, but at least one DPS remained in situ, this was defined as indwelling. Outcomes were  
21 presented as a Hazard Ratio's (HR) using 95% confidence intervals (CI). A 2-sided p-value of <0.05 was  
22 considered statistically significant. Statistical analyses were performed using R software, version 4.2.2.

23

## 1 Results

### 2 Baseline characteristics

3 During the study period, 320 patients underwent ETD for symptomatic WON (114 (35.6%) female, median  
4 age 58 years [IQR: 48.0 – 68.0]). ANP was diagnosed in 306 patients (95.6%) and acute-on-chronic  
5 pancreatitis in 14 (4.4%). Biliary stones were the most common cause of ANP, occurring in 126 patients  
6 (39.4%). In 74% of patients the WON was infected prior to initial ETD. Baseline characteristics are  
7 presented in [Table 1](#).

8

### 9 Endoscopic drainage procedures

10 ETD was performed via trans-gastric route in the majority of patients (n = 291 (90.9%)). A median of two  
11 DPS were placed. In 29 patients (9.1%) LAMS were exchanged to DPS and in three patients (0.9%) a  
12 LAMS was additionally placed in a different WON. Following initial ETD, a nasocystic drain was inserted  
13 in 249 patients (77.8%). An additional necrosectomy was performed in 169 patients (52.8%), with a  
14 median of three necrosectomy procedures [IQR: 2 – 4] in these patients. In 33 patients (10.3%)  
15 percutaneous drainage was performed after ETD and in 13 patients (4.1%) a surgical debridement was  
16 performed. Additional details on the ETD procedures and any additional procedures are presented in  
17 [Table 2](#).

18

19

20

### 20 Stents and long term follow-up

21 Cross-sectional follow-up imaging was performed in 297 (92.8%) patients. During a median follow up of  
22 23 months [IQR: 5.5 – 66.3], a total of 57 patients (17.8%) were diagnosed with a recurrence of a PFC  
23 after initial resolution of ETD treated WON. In patients with a recurrent PFC, resolution of initial WON was  
24 confirmed in all patients on cross-sectional imaging prior to date of diagnosis of a recurrent PFC. In 40/57  
25 (70.2%) patients these were detected at the same location as the initially drained WON. Of all detected  
26 recurrences, 36 (63.2%) were symptomatic, mostly due to infection related complaints. In 24 symptomatic  
27 and one asymptomatic recurrence, additional intervention was indicated, most of the patients underwent  
28 ETD. The remaining PFC recurrences were managed conservatively.

1

1

2 Recurrence rates were different among subgroups of patients in which DPS were removed electively,  
3 DPS had migrated spontaneously, or were left indwelling. During follow-up, 153 of 320 (47.8%) patients  
4 had their DPS removed after a median period of 3.4 months [IQR: 1.6 – 7.0]. The median follow-up period  
5 after stents were removed was 27.1 months [IQR: 4.9 – 79.6]. Recurrence occurred in 39/153 patients  
6 (25.5%). In 27 of 320 patients (8.4%), spontaneous migration of all DPS was documented after a median  
7 follow-up of 7.4 months [IQR: 3.5 – 12.1]. Migration of all DPS was detected by cross-sectional imaging in  
8 all 27 patients. In 4 patients a gastroscopy was performed prior to electively remove the DPS, but upon  
9 inspection the DPS had already migrated spontaneously, after which cross-sectional imaging confirmed  
10 this finding. The median follow-up period after stents migration was 24.7 months [IQR: 5.7 – 48.2].  
11 Recurrence after spontaneous migration of the stents occurred in 4/27 patients (14.8%). In the remaining  
12 140 patients (43.8%), DPS were left in situ until end of follow-up or death (Figure 1), with a median follow-  
13 up of 8.2 months [IQR: 0.6 – 33.8]. Recurrence occurred in 14/140 patients (10%).

14

### 15 **Recurrence and associated factors**

16 In multivariate competing risk regression analysis, both presence of DPDS (HR: 5.08, 95%CI: 1.84 –  
17 14.0) and DPS no longer in situ [HR 3.45, 95%CI: 1.37 – 8.70] were significantly and independently  
18 associated with recurrence of PFC after resolution of WON. Sensitivity analysis for only symptomatic  
19 recurrences showed consistent results, as shown in Supplementary Table 1.

20

### 21 **DPS related complications**

22 In 28 patients all DPS seemed to have migrated spontaneously, including one patient with recurrence  
23 diagnosed 22.7 months prior. In another 28 patients at least one DPS remained in situ after migration of  
24 one or multiple DPS. In one (1.8%) patient, DPS migrated through the WON and resulted in a perforation  
25 of the colon which was located outside the ETD fistula. The patient was treated conservatively by stent  
26 removal and antibiotics. This was diagnosed 9 days after last ETD. No DPS-related complications, such  
27 as occlusion or bleeding after DPS erosion, occurred in the patients with indwelling DPS.

28

2

10

## 1 Discussion

2 In this large, retrospective multicenter study of WON patients, leaving DPS indwelling after successful  
3 ETD is associated with a significantly lower recurrence rate of PFC than after removal or migration of the  
4 DPS. Severe DPS-related complications are rare. These results, in line with recent literature, suggest that  
5 DPS can be considered to be left indwelling to reduce the number of PFC recurrences.

6

7 We found an overall recurrence rate of PFC after successful ETD of 17.8%, of which most were located at  
8 the initial site of WON drainage. In recent literature, these recurrence rates vary widely 0 – 37% [14-27].  
9 Arvanitakis *et al.* compared stent retrieval versus leaving the stents indwelling, and found that retrieval  
10 was associated with higher recurrence rates, with no recurrences in the indwelling group [16]. However,  
11 only 46 patients were included of all types of PFC, and not WON specifically. Bang *et al.* reported similar  
12 findings in all types of PFC [11]. A study from 2013 reported that long-term indwelling stents are safe and  
13 effective with minimal complications [19]. In five patients (16.6%) migration of DPS occurred, resulting in  
14 recurrence of PFC in one patient. In the remaining 25 patients, no recurrence was diagnosed. All of the  
15 abovementioned studies are limited by the small sample size, the relatively short follow-up and competing  
16 risks such as death were not accounted for.

17

18 The study of Chavan *et al.*, however, improved on many of these aspects [14]. After successful ETD and  
19 PFC resolution, the large caliber metal stent was removed and patients diagnosed with DPDS were  
20 randomized between DPS placement or no DPS. In the 104 patients after one year of follow-up, almost  
21 20% of patients presented with a recurrence of PFC. This was not significantly associated with plastic  
22 stents replacement in both intention-to-treat analyses and per-protocol analyses. The trial has some  
23 limitations however, as postulated in three letters to the editor [28-30]. Firstly, the follow-up period  
24 stopped after one year, potentially missing an important part of follow-up as previous studies have shown  
25 that PFC recurrence mostly occurred in the first two years. Secondly, the per-protocol analyses was  
26 hampered by significant differential attrition bias. Thirdly, the protocol of the study was to place a DPS  
27 four weeks after initial LAMS placement, but complete resolution of the WON was not confirmed.

28

1 Several other studies have investigated potential risk factors for recurrence of PFC after initial resolution.  
2 We found DPS removal and/or migration as well as DPDS diagnosis to be significantly associated with  
3 PFC recurrence. Although severely limited by the small cohort of 35 patients, Rana *et al.* found removal of  
4 stents and/or diagnosis of DPDS were independent risk factors for recurrence [31], which was in line with  
5 other recent studies. [11, 16, 26]. Gkolfakis *et al.* found stent migration, CP, and the length of the first  
6 DPS >6 cm to be independent risk factors for recurrence [32]. However, they included all types of fluid  
7 collections and did not routinely remove stents lacking a clear comparison group. The major limitation of  
8 all of these studies is the fact that they have not taken into account competing risks, such as death, and  
9 removal or migration of the stent as a time-varying covariate. However, in the current study we have  
10 performed these exact analyses and have confirmed that DPDS diagnosis and removal or migration of  
11 the DPS are both independently and significantly associated with increased risk of PFC recurrence.

12

13 While recent studies on WON mainly focus on LAMS [33, 34], a recent systematic review and meta-  
14 analysis showed that LAMS and DPS have equal clinical outcomes and adverse events [35]. Recent  
15 prospective studies have shown no significant differences [8-10]. Therefore, more studies are needed  
16 focusing on DPS replacement after WON resolution by LAMS. The need to leave DPS indwelling may  
17 even favor DPS compared to LAMS.

18

19 As compared to the aforementioned studies, our study has several strengths. To the best of our  
20 knowledge, this is the largest study evaluating the clinical outcome of patients after endoscopic treatment  
21 of WON, with regard to the removal of DPS of leaving them in situ. Firstly, patients were included from  
22 three expert treatment centers and thereby including a large number of patients ensuring a high enough  
23 number of events to facilitate multivariable regression analysis. Secondly, with the use of competing risk  
24 analysis the competing event of mortality can be taken into account. Thirdly, time-varying covariates are  
25 more suited for complex situations in patient in which the status of the stent changes over time than  
26 stratification based on what happened in the follow-up. However, with its retrospective design some  
27 inherent limitations are worth noting. Long-term follow-up was not available in several patients as patients  
28 were referred back to another hospital or died shortly after. We took these factors partially into account by

1

1 performing competing risk analysis. Secondly, the definitions of WON were not as well formulated before  
2 the Atlanta guidelines and potential patients could be missed due to misclassification [2]. To obtain our  
3 total cohort, all endoscopically treated PFC were retrospectively analyzed with the most recent guidelines.  
4 Thirdly, the recurrence rate is likely an underestimation as not all patients underwent routine follow-up  
5 imaging to assess this, as shown by the large rate of recurrences who did not undergo a re-ETD.  
6 However, this is likely not to be clinically relevant as these patients would have presented themselves  
7 with symptoms. Also, it is difficult to assess whether a PFC is an actual recurrence, or a PFC/WON at  
8 another location. Fourth, the rate of spontaneous migration of indwelling DPS may have been an  
9 underestimation as follow-up imaging was not routinely performed. Finally, choice of removal or leaving  
10 the DPS indwelling changed over time and differed between treatment centers.

11

12 In conclusion, in this largest study up to date on the effect of removal of DPS after ETD on recurrence  
13 rates of PFC, our results suggest that DPS can be left indwelling indefinitely in order to lower the risk of  
14 (symptomatic) recurrence. The effect of removing or leaving the DPS indwelling, should be included in  
15 future randomized controlled trials with long term follow-up and larger patient cohorts to enable vast  
16 multivariable regression analyses.

17

1

1 **Conflicts of interest**

2 M.J. Bruno received research support from Boston Scientific, Cook Medical, Pentax Medical, Mylan,  
3 ChiRoStim and acts as a consultant/lecturer for Boston Scientific, Cook Medical, Pentax Medical and  
4 AMBU. R.P. Voermans received research funding for investigator initiated studies from Boston Scientific  
5 and Prion Medical. He is a consultant with speakers fee for Boston Scientific. D.M. de Jong, P.M.C.  
6 Stassen, I.G. Schoots, R.C. Verdonk and P.J.F. de Jonge declare that they have no conflicts of interest.

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1

1 **Figure legend**

2 Figure 1. Flowchart of included patients

3 WON = Walled Off pancreatic Necrosis, ETD = Endoscopic Transmural Drainage, IQR = Inter Quartile

4 Range, PFC = Pancreatic Fluid Collection

5 \* = In one patient stents migrated 22.7 months after a recurrence was diagnosed and in one patient

6 stents were removed 11.5 months after recurrence was diagnosed

7

8



| Characteristic  | Multivariate |             |         |
|---|--------------|-------------|---------|
|   | HR           | 95% CI      | p-value |
| Age (in years)  | 0.98         | 0.96 – 1.00 | 0.025   |
| Infected (Yes)*   | 0.47         | 0.24 – 0.93 | 0.030   |
| DPDS diagnosis (Yes)  | 7.06         | 1.82 – 27.4 | 0.005   |
| Stent removal or migration**                                    | 3.91         | 1.07 – 14.3 | 0.039   |
| Stent removal or migration (Yes)**<br>x<br>DPDS diagnosis (Yes) | 0.79         | 0.16 – 3.76 | 0.764   |

**Table S1. Results from multivariate competing risk regression analysis using cause-specific hazard regression for chance of recurrence of symptomatic PFC**

HR = Hazard Ratio, CI = Confidence Interval, ANP = Acute Necrotizing Pancreatitis, DPDS = Disconnected Pancreatic Duct Syndrome, ETD = Endoscopic Transmural Drainage, PFC = Pancreatic Fluid Collection

\* = At baseline or after ETD

\*\* = Analyzed as time-varying covariate

| <b>Characteristic</b>   | <b>Total population (n = 320)</b> | <b>Missing - n (%)</b> |
|---|-----------------------------------|------------------------|
| Sex = Female (%)  | 114 (35.6)                        | 0                      |
| Age in years (median [IQR])   | 58.00 [48.00, 68.00]              | 0                      |
|   |                                   |                        |
| <b>WON characteristics</b>  |                                   |                        |
| Type of Pancreatitis = ANP (%)  | 306 (95.6)                        | 0                      |
| Aetiology of Pancreatitis (%)   |                                   | 0                      |
| - Alcohol   | 57 (17.8)                         |                        |
| - Biliary   | 126 (39.4)                        |                        |
| - Idiopathic  | 78 (24.4)                         |                        |
| - Post-ERCP   | 21 (6.6)                          |                        |
| - Other**   | 38 (11.9)                         |                        |
| WON location (%)  |                                   | 39 (12.2)              |
| - Total   | 94 (33.5)                         |                        |
| - Head  | 38 (13.5)                         |                        |
| - Head + Body   | 32 (11.4)                         |                        |
| - Body + tail   | 39 (13.9)                         |                        |
| - Body  | 35 (12.5)                         |                        |
| - Tail  | 43 (15.3)                         |                        |
| Length in cm (median [IQR])   | 11.71 [8.60, 15.20]               | 31 (10)                |
| Volume (median [IQR])   | 725.20 [402.60, 1483.02]          | 163 (51)               |
| DPDS diagnosis = Yes (%)  | 55 (17.2)                         | 0                      |
| Signs of infection on imaging, fine-needle aspiration, clinical presentation or initial endoscopic findings, prior to ETD = Yes (%) | 182 (74.0)                        | 74 (23.1)              |
|   |                                   |                        |
| <b>Interventions prior to first ETD</b>   |                                   |                        |
| Percutaneous drainage prior to ETD = Yes (%)  | 32 (10.0)                         | 0                      |

|   |         |   |
|---|---------|---|
| Surgical procedure prior to ETD = Yes (%) | 5 (1.6) | 0 |
|---|---------|---|

**Table 1. Baseline characteristics of all included patients**

IQR = Inter Quartile Range, ANP = Acute Necrotizing Pancreatitis, Post-ERCP = Post Endoscopic Retrograde Cholangiopancreatography, WON = Walled Off Pancreatic Necrosis, DPDS = Disconnected Pancreatic Duct Syndrome, ETD = Endoscopic Transmural Drainage

\* = versus acute on chronic pancreatitis

\*\* = Other presumed causes of WON: L-asparaginase (n = 2), Endo-barrier (n = 1), Hypertriglyceridemia (n = 5), ischemia (n = 3), pancreas divisum (n = 2), pancreatic cancer (n = 2), Peutz-Jeghers polyp (n = 1), pharmacological (n = 12), surgery (n = 5), post-partum hypercalcemia (n = 1), post-single balloon enteroscopy (n = 1), systemic lupus erythematosus (n = 1) and traumatic injury (n = 1)

| Characteristic  | Total population (n = 320) | Missing - n |
|---|----------------------------|-------------|
| ETD location (%)  |                            | 0           |
| - Duodenum/Bulbus                                       | 28 (8.8)                   |             |
| - Stomach   | 291 (90.9)                 |             |
| - Oesophagus  | 1 (0.3)                    |             |
| Number of stents at placement (%)                       |                            | 0           |
| - 1   | 13 (4.1)                   |             |
| - 2   | 224 (70.0)                 |             |
| - $\geq 3$  | 83 (25.9)                  |             |
| Total number of endoscopic interventions (median [IQR]) | 2 [1, 4]                   | 0           |
| Nasocystic catheter placed = Yes (%)                    | 249 (77.8)                 | 0           |
| Necrosectomy performed = Yes (%)                        | 169 (52.8)                 | 0           |
| Infection WON = Yes (%)                                 | 66 (20.6)                  | 0           |
|   |                            |             |
| LAMS placement (%)                                      |                            | 0           |
| - Other WON   | 3 (0.9)                    |             |
| - Before DPS placement                                  | 29 (9.1)                   |             |
|   |                            |             |
| <b>Interventions after first ETD</b>                    |                            |             |
| Percutaneous drainage after to ETD = Yes (%)            | 33 (10.3)                  | 0           |
| Surgical procedure prior to ETD = Yes (%)               | 13 (4.1)                   | 0           |

**Table 2. Characteristics of the performed drainage procedures**

ETD = Endoscopic Transmural Drainage, IQR = Inter Quartile Range, WON = Walled Off Pancreatic Necrosis, DPS = Double pigtail stent, LAMS = lumen apposing metal stent



| Characteristic                                | Total population (n = 320) | Missing - n (%) |
|---|----------------------------|-----------------|
| Recurrence = Yes (%)                          | 57 (17.8)                  | 0               |
| - After removal (n = 153)                     | 39 (68.4)                  |                 |
| - After migration (n = 27)                    | 4 (8.8)                    |                 |
| - Indwelling (n = 140)                        | 14 (24.6)                  |                 |
| Time to recurrence in days (median [IQR])     | 370 [198, 767]             | 0               |
| Symptomatic recurrence = Yes (%)              | 36 (63.2)                  | 5 (8.8)         |
| - Mechanic obstruction*                       | 5 (13.9)                   |                 |
| - Inflammation/Infection                      | 26 (72.2)                  |                 |
| Same location as initial WON = Yes (%)        | 40 (70.2)                  | 7 (12.3)        |
| Intervention performed = Yes (%)              | 25 (43.9)                  | 1 (1.8)**       |
| - Re-ETD                                      | 12 (48.0)***               |                 |
| - Percutaneous drainage                       | 9 (36.0)                   |                 |
| - Surgery                                     | 1 (4.0)                    |                 |
| - ERCP with biliary stent placement           | 2 (8.0)                    |                 |
| Total follow-up period in days (median [IQR]) | 690.50 [166.8, 2004.8]     | 0               |
| Death during follow-up = Yes (%)              | 54 (16.9)                  | 0               |

**Table 3. Long-term follow up data**

IQR = Inter Quartile Range

\* = gastric outlet obstruction in three patients, biliary duct compression in two patients

\*\* = Intervention performed elsewhere, unclear whether this was percutaneous or re-ETD

\*\*\* = In 1 patient with asymptomatic recurrence

| Characteristic  | Univariate |             |         | Multivariate |             |         |
|---|------------|-------------|---------|--------------|-------------|---------|
|   | HR         | 95% CI      | p-value | HR           | 95% CI      | p-value |
| Age (in years)  | 0.98       | 0.97 - 1.00 | 0.033   | 0.99         | 0.97 - 1.00 | 0.135   |
| Sex (Female)  | 1.26       | 0.74 - 2.16 | 0.389   |              |             |         |
| ANP (vs acute on chronic)                                       | 0.40       | 0.16 - 1.01 | 0.052   |              |             |         |
| Infected (Yes)*   | 0.52       | 0.31 - 0.90 | 0.018   | 0.61         | 0.35 - 1.05 | 0.076   |
| ETD Location  |            |             |         |              |             |         |
| - Duodenum/bulbus   | Ref        | Ref         | Ref     |              |             |         |
| - Stomach   | 1.40       | 0.51 - 3.88 | 0.513   |              |             |         |
| - Oesophagus  | 0.00       | 0.00 - Inf  | 0.996   |              |             |         |
| Nasocystic catheter (Yes)                                       | 1.04       | 0.54 - 2.02 | 0.902   |              |             |         |
| Necrosectomy (Yes)  | 1.28       | 0.75 - 2.17 | 0.367   |              |             |         |
| Percutaneous intervention (Yes)                                 | 0.98       | 0.49 - 1.94 | 0.951   |              |             |         |
| Surgery intervention (Yes)                                      | 1.82       | 0.83 - 4.02 | 0.138   |              |             |         |
| DPDS diagnosis (Yes)  | 3.82       | 2.26 - 6.45 | <0.001  | 5.08         | 1.84 - 14.0 | 0.002   |
| Stent removal or migration**                                    | 2.66       | 1.43 - 4.93 | 0.002   | 3.45         | 1.37 - 8.70 | 0.009   |
| ETD number (per procedure)                                      | 0.98       | 0.87 - 1.11 | 0.803   |              |             |         |
| Stent removal or migration (Yes)**<br>x<br>DPDS diagnosis (Yes) |            |             |         | 0.87         | 0.26 - 2.88 | 0.819   |

**Table 4. Results from univariate and multivariate competing risk regression analysis using cause-specific hazard regression for chance of recurrence of PFC**

HR = Hazard Ratio, CI = Confidence Interval, ANP = Acute Necrotizing Pancreatitis, DPDS = Disconnected Pancreatic Duct Syndrome, ETD = Endoscopic Transmural Drainage, PFC = Pancreatic Fluid Collection

\* = At baseline or after ETD

\*\* = Analyzed as time-varying covariate

