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ORIGINAL ARTICLE

Routes of nutrition for pancreatic fistula after pancreatoduodenectomy: a prospective snapshot study identifies the need for therapy standardization

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Abstract

The aim of this study is to describe the current utilization of artificial nutrition [enteral (EN) or total parenteral (TPN)] for pancreatic fistula (POPF) after pancreatoduodenectomy (PD). Prospective data of 311 patients who consecutively underwent PD at a tertiary referral center for pancreatic surgery were collected. Data included the use of EN or TPN specifically for POPF treatment, including timing, outcomes, and adverse events related to their administration. POPF occurred in 66 (21%) patients and 52 (79%) of them were treated with artificial nutrition, for a median of 36 days. Forty (76%) patients were treated with a combination of TPN and EN. The median day of artificial nutrition start was postoperative day 7, with a median drain output of 180 cc/24 h. In 33 (63%) patients, artificial nutrition was started while only a biochemical leak was ongoing. Fungal infections and catheter-related bloodstream infection occurred in 13 (28%) and 15 (33%) TPN patients, respectively; among EN patients, 19 (41%) experienced diarrhea not responsive to pancreatic enzymes and 9 (20%) needed multiple endoscopic naso-jejunal tube positioning. The majority of the patients developing POPF after PD were treated with a combination of TPN and EN, with a clinically relevant rate of adverse events related to their administration. Standardization of nutrition routes in patients developing POPF is urgently needed.

Keywords Pancreatic fistula · Pancreatoduodenectomy · Nutrition · Parenteral · Enteral

Introduction

Postoperative pancreatic fistula (POPF) remains the main driver of morbidity after pancreatoduodenectomy (PD), ranging [1] between 5 and 40%, and may cause severe additional life-threatening morbidity like sepsis and bleeding [2]. Attempts to promote fistula closure usually involve prolonged interruption of oral food intake. Therefore, nutritional therapy is a key element of conservative treatment in patients with POPF, consisting in the administration of either total parenteral (TPN) or enteral (EN) nutrition [3].

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The position paper of the International Study Group for Pancreatic Surgery (ISGPS) suggests either EN or fasting with TPN for patients with B and C grade POPF, and oral feeding for those with a biochemical leak (BL) [3, 4]. However, POPF grading is also directly influenced by the administration of nutritional support. Moreover, the final POPF grade is determined by definition "a posteriori", after the complete evolution of its clinical course, despite parameters defining a clinically relevant (B/C) POPF may be present since the early postoperative days. Indications for nutritional therapy during POPF early stages are not clear, despite a prompt administration could potentially influence POPF severity and healing time. Moreover, despite EN is theoretically preferable over TPN, the decision between these two routes remains essentially arbitrary, mainly due to skepticism and lack of evidence about POPF closure timing according to a given route [5, 6]. These two different nutritional therapies may also partially overlap, due to logistical timing required for endoscopic naso-jejunal tube (NJT) positioning or the physiological adaptation to a full EN regimen. Finally,

the occurrence of other postoperative complications (e.g., delayed gastric emptying) may contraindicate the use of EN.

The aim of this prospective snapshot study is to picture the current use of nutritional therapy for POPF after PD at a high-volume pancreatic center. Secondary endpoints are represented by indications, timing, outcomes, and pitfalls of nutrition therapy administration, in the absence of a standardized protocol.

Materials and methods

Study design

Data of consecutive patients undergoing PD from January 1st, 2020, to August 31st, 2021, at the Department of General and Pancreatic Surgery of the Verona University Hospital were prospectively collected. Approval for data collection and analysis for this study was obtained from institutional review board (1101CESC).

Data collection and outcomes

Data regarding general demographic, preoperative, intraoperative, and postoperative characteristics were recorded in a prospectively maintained database built for the purpose of the study. Postoperative outcomes were measured during hospitalization and/or after discharge, up to 90 days after surgery. Timing of postoperative events was expressed in postoperative days (PODs). The Clavien–Dindo classification was used to grade postoperative complications, including clinically relevant POPF (CR-POPF) and BL, post-pancreatectomy hemorrhage (PPH), delayed gastric emptying (DGE), biliary leakage, sepsis, hospital length of stay (LOS), and 90 days mortality [4, 7–11]. Major morbidity was defined as Clavien–Dindo ≥ 3.

Operative procedures

Open PDs were performed in a standardized fashion [12]. Reconstruction was carried out thorough a pancreatico-jejunal, hepatico-jejunal and gastro-jejunal anastomosis using a Child single-loop. A trans-anastomotic externalized stent and/or a surgical jejunostomy were placed in all patients in the high-risk zone according to fistula risk score (FRS), or according to surgeon's preference in case of small main pancreatic duct diameter [13]. Two drains were placed in the proximity of the pancreatic and biliary anastomoses in all patients in a high or intermediate risk zone, and according to the surgeon's discretion in other risk categories. Drains were managed according to previously published protocols [14].

Nutritional therapies

In case of TPN, a standard parenteral nutrition formula was infused through a central venous catheter previously placed intraoperatively in all patients (according to American Society of Anesthesiologists recommendations [15]) to provide at least 2000 kcal/24 h. During the postoperative course, central catheter was replaced if in place for more than 2 weeks. EN was administered either by NJT, placed endoscopically in the efferent jejunal limb during the postoperative course, or by surgical jejunostomy (if present). EN was used to provide at least 2000 kcal/24 h (corresponding to 2000 cc/24 h) if tolerated, through a low-fat, peptide-based enteral feeding formula. Oral feeding was considered as a full standard oral diet. During hospitalization, all patients received specialist evaluation to maintain optimal glycemic control and to assess or treat the occurrence of new onset diabetes or the worsening of pre-existing diabetes. Pancreatic exocrine insufficiency was treated with oral supplementation of pancreatic enzymes if needed.

When nutritional therapy (EN or TPN) was specifically administered for POPF treatment, further data were prospectively retrieved in terms of: (1) time of POPF onset and resolution (defined as drain removal, or output < 20 cc for > 48 h with no relapse), (2) time of full oral diet introduction and restart in case of discontinuation, (3) type, timing and duration of nutritional therapy, (4) drain output (ml) at POPF appearance and at nutritional therapy introduction, (5) EN and TPN overlap and duration (if present). Additional outcomes related to nutritional therapy were: (1) presence of candidemia or ß-D-glucan > 80 pg/ml, (2) presence of catheter-related bloodstream infection (CRBSI) (defined according to the Infectious Diseases Society of America [16]), (3) presence of EN-related diarrhea (defined as diarrhea not responsive to pancreatic enzymes supplementation and responsive to EN interruption), (4) number of endoscopic NJT repositioning, (5) jejunostomy-related complications and (6) median daily EN infusion.

Statistical analysis

Considering an expected POPF rate of 20% [17], a sample size of 300 consecutive PDs was calculated to include at least 60 POPF patients. Continuous variables were expressed as means with standard deviations (SD) or as medians with range, whenever appropriate. Student's *t* test was used to compare means between groups. Nonparametric tests were used when appropriate. Chi-square test was used for categorical data. All tests were 2-tailed. *P* values < 0.05 were considered statistically significant. Statistical analysis was performed with SPSS software (SPSS Inc., version 20 for Macintosh, IBM, Chicago, IL, USA).

Results

A total of 311 PDs were collected. Patients' characteristics are summarized in Table 1. POPF occurred in 66 (21%) patients: 8 (12%) developed a BL, 51 (77%) a grade B and 7 (11%) a grade C POPF, with a total of 58 (19%) patients developing CR-POPF. Major morbidity (Clavien–Dindo ≥ 3) developed in 52 patients (17%). The overall mortality rate was 3% ($n = 11$). During the postoperative course, 75 (24%) patients were treated with EN and 101 (32%) with TPN for any indication.

POPF characteristics and nutrition strategies

The clinical characteristics and nutrition strategies analyzed among the 66 patients who experienced POPF are displayed in Table 2 and Fig. 1. The median day of full oral diet introduction after surgery was POD 4, while the median day of POPF appearance was POD 5, with a median drain output of 50 cc/24 h. All patients with BL (by definition), and only 6 (12%) with B grade POPF, were treated with oral diet only. A total of 52 (79%) patients with POPF were treated with artificial nutrition (specifically for this complication), 45 (88%) with B grade and 7 (100%) with C grade POPF, for a median duration of 36 days. The median day of artificial nutrition start was POD 7, and the median drain output when artificial nutrition was started was 180 cc/24 h. In 33 (63%) patients, the ongoing process was still at the BL step until artificial nutrition was started, while 18 (35%) already had a grade B and 1 (2%) a grade C POPF. The median POPF duration was 23 days, with a POPF closure rate of 68% at 30 days.

Artificial nutrition and POPF

Among 52 patients treated with artificial nutrition for POPF, 6 (12%) were treated with TPN only and 6 (12%) with EN only, while 40 (76%) were treated with a combination of both, either separately (5%) or with some degree of overlap (71%) (Table 3). When it occurred, TPN and EN overlap lasted for a median of 7 days. TPN was started before EN in 70% of patients. Overall, TPN was generally started in POD 8 for a median duration of 14 days, while EN was started in POD 12 for a median duration of 17 days. The "typical" clinical course of patients undergoing artificial nutrition for POPF, based on 37 (71%) patients with POPF experiencing an overlap between TPN and NE, is pictured in Fig. 2.

Adverse events related to artificial nutrition

Adverse events related to artificial nutrition for POPF are reported in Table 4. Thirteen (28%) patients treated with

Table 1 Preoperative, intraoperative and postoperative profile of all patients who underwent PD during the study period ($N = 311$)

Characteristics	Total, no. (%)
Preoperative	
Age, median (range), years	65 (17–84)
Female sex	157 (50)
BMI, median (range)	24 (16–37)
Smoker	147 (47)
Diabetes	64 (21)
Weight loss	134 (43)
Ischemic cardiac disease	11 (4)
Hypertension	128 (41)
COPD	17 (5)
Chronic renal failure	7 (2)
ASA score	
1–2	244 (78)
3–4	67 (22)
Jaundice palliation	177 (57)
Preoperative multidrug-resistant bacterial colonization	39 (13)
Neoadjuvant therapy	154 (50)
Presumed diagnosis	
PDAC/chronic pancreatitis	199 (64)
Duodenal/ampullary/cystic/NET	112 (36)
Intraoperative	
Surgery type	
Pylorus preserving	252 (81)
Whipple	59 (19)
Pancreatic anastomosis	
PJ	308 (99)
PG	3 (1)
Externalized pancreatic stent	115 (37)
Feeding jejunostomy	13 (4)
Blood loss	
≤ 400 ml	114 (37)
401–700 ml	91 (29)
701–1000 ml	64 (21)
> 1000 ml	42 (13)
Intraoperative transfusion	48 (15)
Drainless	16 (5)
FRS zone	
1 (0–2)	107 (34)
2 (3–6)	164 (53)
3 (7–10)	39 (13)
Postoperative	
POPF	66 (21)
CR-POPF	58 (19)
POPF grade	
BL	8 (12)
B	51 (77)
C	7 (11)
Biliary fistula	35 (11)

Table 1 (continued)

Characteristics	Total, no. (%)
DJ/GJ fistula	12 (4)
Chyle leak	8 (3)
PPH	49 (16)
DGE	46 (15)
Sepsis	68 (22)
Postoperative pneumonia	36 (12)
Re-intubation	22 (7)
Cardiac complication	25 (8)
Percutaneous drainage	25 (8)
Enteral nutrition	75 (24)
TPN	101 (32)
Postoperative octreotide	23 (7)
Antibiotics	114 (37)
Re-laparotomy	24 (8)
ICU admission	29 (9)
ICU stay, median (range), days	8 (2–105)
Externalized pancreatic stent malfunction	17 (15[a])
Drain removal, median (range), days	5 (3–169)
Discharged with drains	16 (5)
LOS, median (range), days	11 (6–183)
Readmission	33 (11)
Clavien–Dindo	
0	115 (37)
1	29 (9)
2	93 (30)
3a	21 (7)
3b	15 (5)
4a	19(6)
4b	8 (3)
5	11 (3)
Clavien–Dindo ≥ 3	52 (17)
Mortality	11 (3)

BMI body mass index, *COPD* chronic obstructive pulmonary disease, *ASA* American Society of Anesthesiologists, *PDAC* pancreatic ductal adenocarcinoma, *NET* neuro-endocrine tumor, *PJ* pancreatico-jejunostomy, *PG* pancreaticogastrostomy, *FRS* Fistula Risk Score, *POPF* postoperative pancreatic fistula, *BL* biochemical leak, *POAP* postoperative acute pancreatitis, *DJ* duodenal–jejunal anastomosis, *GJ* gastro-jejunal anastomosis, *PPH* post-pancreatectomy hemorrhage, *DGE* delayed gastric emptying, *TPN* total parenteral nutrition, *ICU* intensive care unit, *LOS* length of hospital stay

[a]Considering only patients who underwent pancreatic stent positioning

TPN for POPF had candidemia (or ß-D-Glucan > 80 pg/ml) during the postoperative course, while 15 (33%) developed CRBSI. Among patients treated with EN for POPF, 19 (41%) experienced EN-related diarrhea and 9 (20%) required multiple endoscopic NJT positioning. No adverse event related to jejunostomy was registered among the 13 patients in which it was present. The median EN infusion was 1300 cc/day, corresponding to 1300 kcal/day.

Discussion

The present study pictures the arbitrary use of artificial nutrition once POPF occurs after PD in the setting of a tertiary referral center, due to the absence of high-level evidence or established protocols standardizing its administration.

Nearly all patients developing CR-POPF after PD were treated with artificial nutrition. In detail, artificial nutrition was usually the first clinically relevant management change, introduced in the setting of a BL with an elevated drain output after the first postoperative week, and maintained for a median of 1 month, which was also the median time required for POPF closure. TPN and EN were often used together, with some degree of overlap, making it difficult to segregate their actual clinical outcomes. Of note, adverse events related to artificial nutrition routes were not uncommon, especially during TPN.

Artificial nutrition is considered a cornerstone in the conservative treatment of POPF. An oral food intake is believed to increase the production of pancreatic juice and the activation of trypsinogen, possibly exacerbating the fistula, despite it is unknown on what measure this applies to patients after PD [18]. As TPN does not stimulate pancreatic secretion, it remains a reasonable solution when prolonged nutritional support is needed without increasing the exocrine pancreatic function. However, long-term TPN leads to infectious complications and negative functional and morphological changes, not only within the gastrointestinal mucosa, but also the exocrine pancreas itself [19]. Conversely, EN introduced directly into the jejunum and ileum is presumed to maintain a negative feedback inhibition of pancreatic exocrine secretion [20]. Moreover, EN has lower costs and the potential advantage of avoiding infectious and metabolic complications related to the parenteral route. The potential advantages of EN over TPN are supported in particular by a randomized controlled trial showing a higher 30-day POPF closure rate in case of EN, compared with fasting plus TPN [5]. However, the above-mentioned trial included distal pancreatectomies and other types of gastrointestinal surgeries other than PD, and the inclusion criteria in terms of POPF severity (B grade only) were unclear and based on an outdated ISGPS definition. As shown in the present study, these two routes of artificial nutrition are rarely used separately in clinical practice, and it is therefore difficult to assess the superiority (or non-inferiority) of one above the other outside the setting of

Table 2 Clinical characteristics and nutrition strategies in patients with POPF ($N=66$)

Characteristics	Total, *N.* (%)	POPF grade (%)		
		BL = 8 (12)	*B* = 51 (77)	*C* = 7 (11)
Full oral diet introduction, POD, median (SD)	4 (17)	3 (2)	4 (15)	31 (32)
Day of appearance, POD, median (SD)	5 (5)	5 (3)	5 (6)	3 (1)
Drain output at appearance, ml/24 h, median (SD)	50 (129)	35 (35)	50 (130)	300 (140)
Duration, days, median (SD)	23 (29)	7 (5)	25 (17)	41 (62)
30-days resolution	45 (68)	8 (100)	35 (69)	2 (29)
Nutrition route				
Oral diet only	14 (21)	8 (100)	6 (12)	0
Artificial nutrition	52 (79)		45 (88)	7 (100)
Artificial nutrition start, POD, median (SD)	7 (7)[a]		8 (7)[a]	6 (7)[a]
Drain output at artificial nutrition start, ml/24 h, median (SD)	180 (100)[a]		100 (185)[a]	300 (125)[a]
POPF grade at artificial nutrition start				
BL	33 (63)[a]			
B	18 (35)[a]			
C	1 (2)[a]			
Artificial nutrition duration, days, median (SD)	36 (63)[a]		31 (28)[a]	58 (148)[a]
Oral diet restart after discontinuation, POD, median (SD)	31 (29)[a]		31 (14)[a]	109 (94)[a]

POD postoperative day, *POPF* postoperative pancreatic fistula, *BL* biochemical leak

[a]Considering only 52 patients treated with artificial nutrition

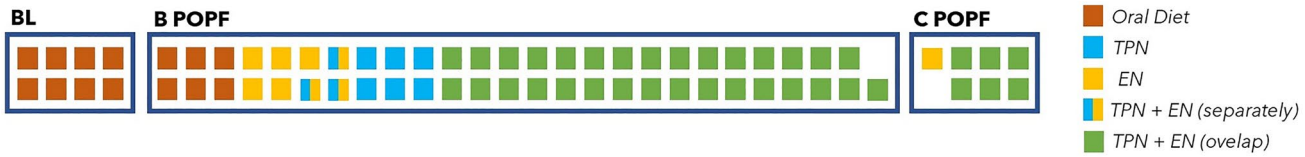

Fig. 1 Routes of nutrition in all patients developing POPF after PD ($N=66$)

an updated controlled study, which remains highly needed. In the present series, TPN was affected by high rates of CRBSI and fungal infections. On the other hand, EN presented limitations related to patients' tolerance, with high rates of diarrhea unresponsive to pancreatic enzymes supplementation and a suboptimal provision of daily kcal intake (1300 kcal/day), requiring some amount of imbrication with TPN most of the times. The optimal way of EN administration is also unclear, but post-pyloric/intrajejunal placement of the feeding tube is strongly advocated by the ISGPS to avoid risk of aspiration in patients with DGE or gastric outlet obstruction [3]. There are various techniques for post-pyloric EN administration, all with their specific disadvantages [3]. The institutional policy of the present pancreas unit does not consider the routine intraoperative placement of a jejunostomy or an NJT in all PD, but only in few selected patients with elevated POPF risk and/or signs of bowel congestion. However, as the blind placement of feeding tubes beyond the pylorus in the postoperative days is frequently unsuccessful, in patients requiring EN the NJT was placed with the aid of endoscopic guidance. The logistical timing required for endoscopic NJT positioning, together with the slow physiological adaptation to a full EN regimen, explains the large degree of overlap between TPN and EN. The logistic advantages of the administration of EN simply via a naso-gastric tube in patients with low risk of aspiration should be therefore considered in the future, aiming to decrease the need for TPN imbrication and related adverse events.

Only a minority of patients with grade B POPF (12%) were treated with oral diet only, compared to all patients with BL (as for the ISGPS definition). However, the borders of such a distinction become of little value, as it should be noted that two-thirds of patients were still classified as BL when artificial nutrition was started. Moreover, only a minority (21%) of patients presenting with POPF were eventually treated with oral diet only, and the typical clinical scenario of a patient starting artificial nutrition comprises a high daily output of amylase-rich drain fluid within the first postoperative week. A recent trial has shown how oral

Table 3 Artificial nutrition in patients with POPF ($N=52$)

Characteristics	Total, no. (%)
Artificial nutrition type	
EN only	6 (12)
TPN only	6 (12)
TPN + EN (overlapping)	37 (71)
TPN + EN (separately)	3 (5)
TPN start, POD, median (SD)	8 (12)
TPN duration, days, median (SD)	14 (24)
EN start, POD, median (SD)	12 (8)
EN duration, days, median (SD)	17 (29)
Artificial nutrition sequence	
EN first	9 (22)[a]
TPN first	28 (70)[a]
Starting contemporarily	3 (8)[a]
Overlap duration, days, median (SD)	7 (21)[b]

POD postoperative day, *POPF* postoperative pancreatic fistula

[a]Considering only 40 patients treated with both TPN and EN (separately or overlapping)

[b]Considering only 36 patients with overlapping TPN/EN

feeding in patients with POPF after PD did not increase the duration or grade of POPF compared to EN, but was associated with reduced duration of stay and hospital costs [6]. These results were similar to the findings of Fujii and colleagues, who compared a group of patients treated with oral diet to another group maintained on TPN after the occurrence of POPF, analyzing the effect of oral food intake on the healing process of POPF [21]. Despite a greater volume of pancreatic drain output in the oral dietary intake group, the progression to more a clinically relevant POPF or related complications was not different. These data support the concept that oral feeding does not exacerbate POPF. However, these results must be carefully interpreted, as most of the patients of both trials were included very early in their postoperative course (POD 3 and POD 5, respectively). In a real-life scenario, patients undergo artificial nutrition when POPF is persistent and with high drain fluid volume, after a "failed" attempt of a full oral diet in the first postoperative days.

This study has several limitations. Due to its purely observational nature, its aim was exclusively to provide a "real-life" picture of the use artificial nutrition in a high-volume center for pancreatic surgery. This practice revealed to be

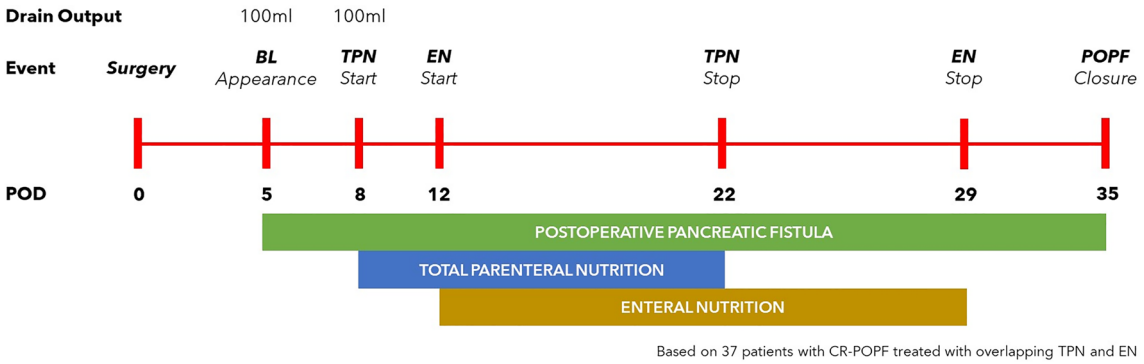

Fig. 2 "Standard" clinical course of a clinically relevant POPF after PD treated with artificial nutrition

Table 4 Adverse events related to artificial nutrition in patients with POPF

TPN	Total, no. (%) ($N=46$)
Candidemia or ß-D-glucan > 80 pg/ml	13 (28)
CRBSI	15 (33)
EN	**Total, no. (%) ($N=46$)**
EN-related diarrhea	19 (41)
Need of endoscopic NJT repositioning	9 (20)
Jejunostomy-related complications[a]	0[a]
Daily EN infusion, cc, median (SD)	1300 (580)

CBRSI catheter-related bloodstream infection, *NJT* naso-jejunal tube

[a]Among 13 patients with surgical jejunostomy

arbitrary, not following standardized pathways or definite patient selection, and also presenting a high degree of overlap between treatments. Therefore, it is not possible to draw any definitive conclusion from this study on how and when patients with POPF should be treated with artificial nutrition. This knowledge gap in pancreatic surgery remains, and it can probably be solved only by future studies with intention-to-treat protocols, standardized nutritional interventions and strict inclusion criteria.

In conclusion, despite no clear evidence showing the benefit of avoiding oral intake or recommendations regarding proper indications, artificial nutrition is widely used in patients experiencing POPF after PD, with a significant rate of related adverse events. Further evidence arising from controlled trials is urgently needed and should target those individuals with criteria consistent with a clinically relevant evolution of POPF after oral diet introduction.

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Data availability The data that support the findings of this study are available on request from the corresponding author, CB.

Declarations

Conflict of interest The authors declare that they have no conflicts of interest to declare.

Ethical approval This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee of the University of Verona approved this study with the number: 298CESC.

Informed consent All patients signed a written informed consent to be included in the clinical data registry (PAD-R) recording information to be used for prospective or retrospective studies.

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