

Definition and classification of chyle leak after pancreatic operation: A consensus statement by the International Study Group on Pancreatic Surgery

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Background. Recent literature suggests that chyle leak may complicate up to 10% of pancreatic resections. Treatment depends on its severity, which may include chylous ascites. No international consensus definition or grading system of chyle leak currently is available.

Methods. The International Study Group on Pancreatic Surgery, an international panel of pancreatic surgeons working in well-known, high-volume centers, reviewed the literature and worked together to establish a consensus on the definition and classification of chyle leak after pancreatic operation.

Results. Chyle leak was defined as output of milky-colored fluid from a drain, drain site, or wound on or after postoperative day 3, with a triglyceride content ≥ 110 mg/dL (≥ 1.2 mmol/L). Three different grades of severity were defined according to the management needed: grade A, no specific intervention other than oral dietary restrictions; grade B, prolongation of hospital stay, nasoenteral nutrition with dietary restriction, total parenteral nutrition, octreotide, maintenance of surgical drains, or placement of new percutaneous drains; and grade C, need for other more invasive in-hospital treatment, intensive care unit admission, or mortality.

Conclusion. This classification and grading system for chyle leak after pancreatic resection allows for comparison of outcomes between series. As with the other the International Study Group on Pancreatic Surgery consensus statements, this classification should facilitate communication and evaluation of different approaches to the prevention and treatment of this complication. (Surgery 2016;■:■-■.)

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CHYLE LEAK (CL) is a well-recognized and potentially serious complication after abdominal operation. Recent literature suggests that intra-abdominal CL, which includes chylous ascites as well, may occur in up to 10% of patients after pancreatic resections.¹ Due to increasing numbers of extended resections being performed, the incidence of CL might increase further.

Chyle is the lymphatic fluid in the wall of the bowel consisting of an emulsion of lymph and triglyceride fat (chylomicrons); chyle is transported from the lymphatic vessels in the wall of the intestine to the lymphatic vessels in the mesentery, where they coalesce into the cisterna chyli, which joins the thoracic duct to drain into the venous circulation.² The cisterna chyli and its major branches, located anterior to the first and second lumbar vertebrae at the same level of the pancreatic head and neck, may be injured during pancreatic resections, especially pancreatoduodenectomy.^{3,4} CL may induce malnutrition and lead to an immune compromised state.⁵

The International Study Group of Pancreatic Surgery (ISGPS) has introduced several international consensus definitions and grading systems for the most common complications of pancreatic operation, including pancreatic fistula, delayed gastric emptying, and postpancreatectomy hemorrhage, and consensus definitions for borderline resectable pancreatic cancer, pancreatic anastomoses, extended resections, and standard lymphadenectomy.⁶⁻¹² These grading systems have been well accepted and adopted in the literature and have been used extensively to allow accurate comparison of outcomes across institutions and countries.

Intra-abdominal CL seems to occur primarily after pancreatic resection, but the reported incidence varies widely, probably due to a lack of uniformity in definitions of CL.¹³⁻¹⁵ Using strict criteria, a recent large series demonstrated the

presence of a CL in 12.5% of patients after pancreatoduodenectomy and found that initial and maximum drainage volumes were associated with the duration of hospital stay and time to resolution of CL.¹ A uniform and, more importantly, an objective definition of CL does not exist. Furthermore, there is no consensus on an optimal treatment strategy for CL and chylous ascites. Restriction of long-chain triglycerides by a low-fat diet or total parenteral nutrition (TPN) will decrease lymph flow, thus decreasing the volume of the CL with eventual resolution. Medium-chain-triglycerides (MCT) often are introduced in the low-fat diet, because these MCTs are not absorbed via the gut lymphatics and help to increase the calorie intake of the patient. MCT can be transported across the enterocyte and into the mesenteric venous circulation; this process does not require transport into the mesenteric lymphatics.¹⁶

The aim of the ISGPS was to develop a universal, objective definition, classification, and grading system for CL after pancreatic operation. Such a definition should allow valid assessment and comparison of studies across institutions and countries regarding this complication.

METHODS

An in-depth review of the literature on CL after pancreatic operation was performed by the ISGPS, an international panel of pancreatic surgeons all working in well-known, high-volume centers and each with considerable clinical and scientific experience.

A systematic search of the PubMed and the Cochrane electronic databases was performed in July 2015, including the terms “chylous ascites” and “chyle” in the medical subject headings. An additional free search term limited results to articles related to the pancreas. Terms were combined with Boolean operators. A non-MeSH search also was performed. Studies of any design investigating

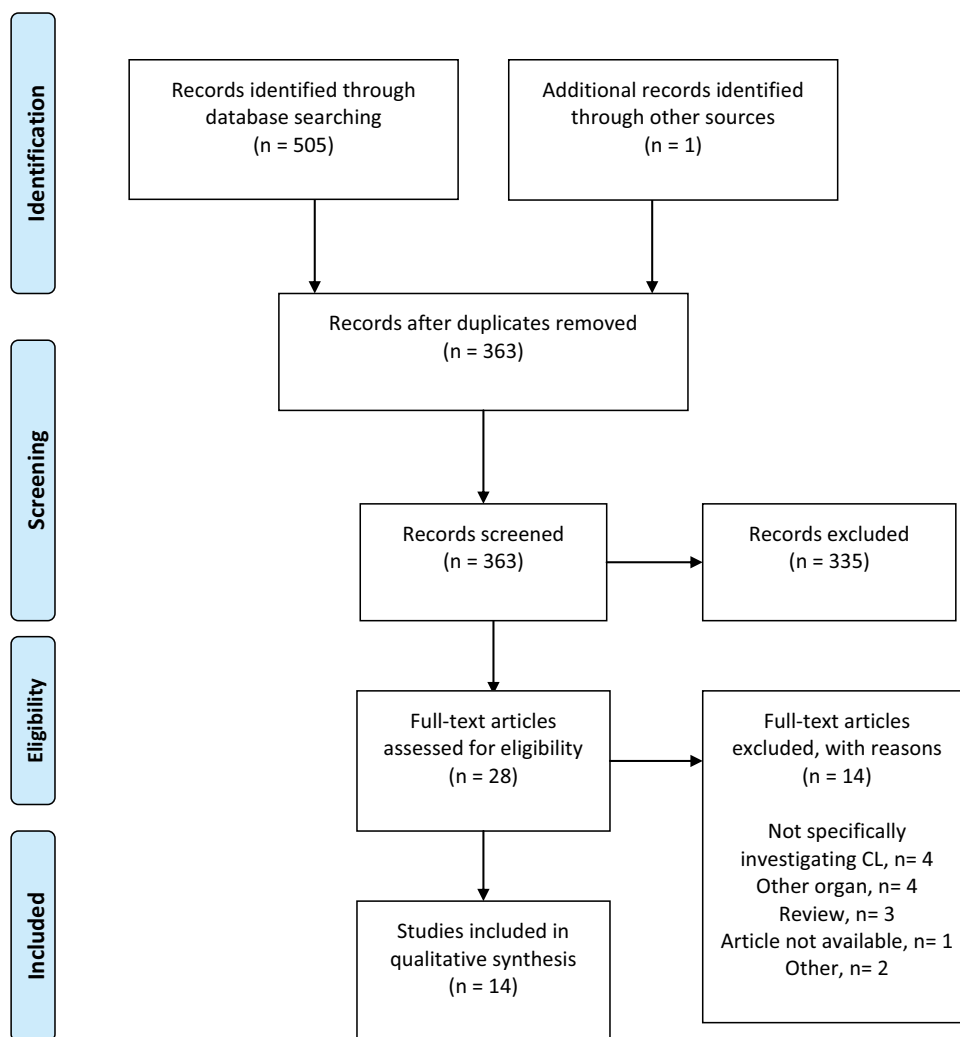


Fig. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

specifically CL after pancreatic resection also were included. The language of the selected articles was limited to English. Case reports were included to capture potentially rare but effective novel treatment strategies for uncontrolled CL. The title and abstract and subsequently the full-text articles of all potentially relevant studies were screened for relevance by 2 independent reviewers (L.B.R. and R.S.). Reference lists and related articles in PubMed of all included articles were reviewed to ensure no relevant studies were missed. Discrepancies were discussed, and any doubts were resolved through discussion with a third author (M.G.B. or D.J.G.). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed.¹⁷

The first concept of the review and a suggested definition was circulated to all ISGPS participants. All authors were required to provide substantial

feedback on the manuscript or consensus definition. Comments or suggestions were gathered and discussed within a dedicated subgroup, after which a new version was composed and again circulated to all participants; relevant comments from the members of the ISGPS were gathered again and included in subsequent drafts until, after 6 versions during a period of 9 months, a final consensus statement was reached and confirmed by all authors. All feedback of participants to the coordinators was discussed routinely by other ISGPS members via e-mail.

Assessment of methodological quality. The methodologic quality of included studies was assessed. All studies were graded according to the evidence-based library and information practice critical appraisal checklist developed by Glynn.¹⁸ An overall validity calculation of $\geq 75\%$ indicates

Table I. Study characteristics of chyle leaks after pancreatic operation

Study	Year	Country	Design	No. patients	Validity (%)
Pan et al ¹⁹	2015	China	Retrospective cohort study	1,921	95
Corradini et al ²⁰	2015	Germany	Case report	1	Case report
Abu Hilal et al ¹⁵	2013	UK	Retrospective cohort study	245	95
Kim et al ²¹	2013	South Korea	Retrospective cohort study	222	90
Kuboki et al ²²	2013	Japan	Retrospective cohort study	574	90
Noji et al ²³	2012	Japan	Retrospective cohort study	138	90
D'Hondt et al ²⁴	2011	Belgium	Case report	1	Case report
Aoki et al ²⁵	2010	Japan	Retrospective and prospective cohort study	86	86
Van Der Gaag et al ²⁶	2008	The Netherlands	Retrospective cohort study	609	95
Assumpcao et al ¹⁴	2008	USA	Match-controlled cohort study	3,532	86
Malik et al ²⁷	2007	UK	Retrospective cohort study	105	85
Madanur et al ²⁸	2007	UK	Retrospective cohort study	138	84
Kollmar et al ²⁹	2000	Switzerland	Case report	1	Case report
Cope ³⁰	1998	USA	Prospective cohort (feasibility) study	1	Case report

that the study can be regarded as valid. We did not assess the methodological quality of case reports.

RESULTS

Literature review. The search revealed 505 studies, 14 of which were eligible for data extraction. The Figure depicts the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for study selection. Table I depicts general study characteristics.^{14,15,19-30} From a total of 7,574 patients undergoing pancreatic resection, 224 patients (3.0%) were reported to have developed a CL; the incidences across individual studies ranged from 1–16%.

Definitions. Nine studies reported a definition for CL after pancreatic resection (Table II). Although similar, none of the studies adhered to the same definition. Most studies incorporated the appearance of drainage fluid (milky/white) and assessment of the triglyceride concentration in the fluid ranging from ≥ 110 to >130 mg/dL (1.2–1.4 mmol/L). The volume of drainage (if an intra-abdominal drain was present) also was noted often, with different cut-off values ranging between ≥ 100 mL and >600 mL per day.

Independent risk factors. Three studies identified early enteral feeding as an independent risk factor for the onset of CL.²¹⁻²³ Dissection of the para-aortic area was identified as a risk factor for development of CL in 2 studies, as were the extent of lymph node dissection, the presence of retroperitoneal invasion, chronic pancreatitis, and total number of lymph nodes harvested.^{14,15,19,22,26} Other identified independent risk factors included dissection in the area of the root of the superior mesenteric artery, lymphovascular invasion, neoadjuvant therapy,

vascular resection, female sex, and postoperative portal or mesenteric venous thrombosis.^{15,19,26}

Management. CL usually was recognized at a median of 5–6 days postoperatively. Of the 224 patients who developed CL, 24 (11%) patients did not receive any specific treatment and recovered uneventfully.^{21,26} Primary treatment consisted most often of oral/enteral dietary measures (53%, $n = 119$) or TPN (51%, $n = 114$).^{14,21-23,25-27}

The pooled success rate of CL treatment across all included studies was 95% (213/224 patients). Five studies did not report a 100% success rate. In 1 study, 7 of 47 patients treated with TPN or octreotide required additional lymphoscintigraphy, lymphangiography, sclerotic (ie, lymphatic) embolization, or reoperation.¹⁴ In another study, 1 of the 7 patients treated with TPN eventually was treated successfully with a peritoneovenous shunt.²⁷ In a case report of 1 patient, radiation treatment seemed to be successful when TPN failed.²⁰ One out of 3 patients treated with abdominal paracentesis and MCT-diet alone required additional TPN in 1 study, and in a final older case report percutaneous transabdominal catheterization of the cisterna chyli failed and the patient subsequently underwent successful peritoneovenous shunt insertion.^{28,30}

Dietary measures included a low-fat diet with restriction of long-chain triglycerides (46%), an MCT diet (40%), and a fat-free diet (3%).^{14,15,21,26,28}

In 1 study, octreotide was combined with TPN in 5 patients.²⁵ Three studies noted that somatostatin had been used perioperatively in an attempt to decrease the incidence of pancreatic leak after the pancreatectomy.^{15,26,27} Three studies used routine, early postoperative enteral feeding during the study period.^{23,26,27}

Table II. Definitions and incidence of chyle leak after pancreatic operation

Study	Drain volume	Appearance of fluid	Triglyceride concentration in fluid	Other findings in the fluid	Incidence
Pan et al ¹⁹	≥100 mL/d	Milky or creamy	≥110 mg/dL	Noninfectious	3%
Corradini et al ²⁰	—	—	—	—	Case report
Abu Hilal et al ¹⁵	>200 mL/d	Milky	>130 mg/dL	Amylase normal	16%
Kim et al ²¹	Any	Milky	>110 mg/dL	—	11%
Kuboki et al ²²	≥100 mL/d	Milky	≥110 mg/dL	Amylase-free	3%
Noji et al ²³	—	Milky	>110 mg/dL	Onset of drainage with start of enteral feeding Decrease in volume of drainage with discontinuing enteral feeds	8%
D'Hondt et al ²⁴	—	—	—	—	Case report
Aoki et al ²⁵	—	Milky, non-purulent	>110 mg/dL	—	7%
Van Der Gaag et al ²⁶	≥275 mL/d	Milky	>110 mg/dL	Onset of drainage with start of enteral feeding	11%
Assumpcao et al ¹⁴	≥200 mL/d	Milky	≥110 mg/dL	Low amylase	1%
Malik et al ²⁷	>600 mL/d	—	—	Amylase-free Contains chylomicrons Bile-free	7%
Madanur et al ²⁸	—	—	—	—	2%
Kollmar et al ²⁹	—	—	—	—	Case report
Cope ³⁰	—	—	—	—	Case report

Complications. Four studies identified an increase in hospital stay associated with the CL, but not all studies addressed hospital stay.^{15,23,25,26} In 1 study, CL was associated with a significantly greater duration of abdominal drainage (14 vs 10 days) and an increased incidence of portal or mesenteric venous thrombosis (8% vs 2%).¹⁵ Other associated complications of CL were reported; in 1 study of 86 patients, complications included malnutrition defined as serum albumin <3.5 mg/dL (92%), sepsis (13%), peritonitis (6%), abscess (4%), and concomitant pancreatic fistula (4%).¹⁴ In another study 1 of 3 patients was unable to receive adjuvant chemotherapy due to poor health caused by the CL.²⁸ The ability or lack thereof in receiving adjuvant chemo- and or radiotherapy was not addressed in the other studies.

Consensus definition. Based on the findings, the ISGPS proposes the following definition of CL after pancreatic operation with the grading system outlined in Table III. CL is defined as the output of milky-colored fluid from a drain, drain site, or wound, on or after postoperative day 3, with a triglyceride content ≥110 mg/dL or ≥1.2 mmol/L. Three different grades (A, B, and C) were defined according to the clinical

scenario, management, and duration of hospital stay. The proposed definition and grading system applies to isolated CL. In the event of other, simultaneous complications, such as high amylase levels in case of postoperative pancreatic fistula as described by the ISGPF, both grading systems should be used in combination.⁶

Grade A implies a clinically irrelevant CL. There should be no prolongation of hospital stay and a conservative approach with only restrictions in the oral diet.

Grade B requires that 1 of the following criteria is fulfilled: nasoenteral nutrition with dietary restriction and/or TPN, percutaneous catheter drainage by interventional radiology or maintenance of the surgical drains, or drug treatments (eg, octreotide) to control the CL. Grade B results in a prolonged hospital stay related directly to the CL. A patient might be discharged with the surgical drain in situ or be readmitted for CL.

Grade C requires more invasive treatment such as by interventional radiology involving lymphatic embolization/sclerosis, admission to an intensive care unit, operative exploration and peritoneovenous shunt, or implies mortality directly due to the CL. Patients readmitted for management of CL for

Table III. ISGPS consensus definition and grading system for isolated chyle leak after pancreatic resection

CL is defined as the output of milky-colored fluid from a drain, drain site, or wound, on or after postoperative day 3, with a triglyceride content ≥ 110 mg/dL or ≥ 1.2 mmol/L.

	Grade A	Grade B	Grade C
Therapeutic consequence	None or oral dietary restrictions*	Nasoenteral nutrition with dietary restriction* and/or TPN, percutaneous drainage by IR, maintenance of surgical drains, or drug (eg, octreotide) treatment	Other invasive in-hospital treatment,† admission to the intensive care unit, and/or mortality‡
Discharge with (surgical) drain or readmission‡	No	Possibly	Possibly
Prolonged hospital stay‡	No	Yes	Yes

*No-fat diet with/without medium-chain-triglyceride.

†Interventional radiology (excluding percutaneous drainage) or reoperation.

‡Related directly to the chyle leak.

TPN, total parenteral nutrition; IR, Interventional radiology.

these more invasive approaches change from a grade B to a grade C CL.

DISCUSSION

The present ISGPS consensus statement provides a definition for CL after pancreatic operation, which is intended to be all-inclusive, as objective as possible, and applicable to all situations, including chylous ascites. Such a universal definition should allow for better comparison of outcomes between centers and should facilitate new studies concerning this relatively rare but clinically relevant complication of pancreatic operation. Fundamental in the development of the classification system was the clinical relevance of each criterion and classification to the patient directly. As in previous ISGPS statements, a full systematic review was performed including a total of 7,574 patients undergoing pancreatic resection in which the incidence of CL was available.

The definition of CL in the literature varied but most often incorporated the triglyceride concentration, appearance, and daily volume of CL (when an intra-abdominal drain was present). The ISGPS agreed that CLs are relevant, regardless of a minimal reported volume threshold. Furthermore, previous ISGPS definitions rely on a threshold to define the presence of the definition which reflects a physiologic alteration (eg, an increased level of the drain amylase activity) rather than volume.⁶ A volume threshold was therefore not incorporated into our definition of CL. In patients with a low oral/enteral intake, triglyceride concentration may be less than the cut-off of 110 mg/dL or 1.2 mmol/L, thus leading to a slight

underestimation of the incidence of CL. Because duration of hospital stay after pancreatic operation depends strongly on local, cultural, regional aspects, we focused on “prolonged hospital stay” rather than on providing an absolute duration of hospital stay cut-off.

Some hospital laboratories may determine the presence of chylomicrons in drainage fluid instead of triglyceride content. Generally speaking, when chylomicrons are detected, the drainage fluid triglyceride content will exceed 110 mg/dL. As such, the presence of chylomicrons in drainage fluid may be regarded in these centers equal to a triglyceride content >110 mg/dL.

In most series, initial noninterventional treatment of CL with dietary restrictions was successful. No study reported exactly how the response to treatment was measured (eg, through imaging or based on clinical parameters such as progressive decrease in volume of drainage or concentration of triglyceride). Complication rates were low, although 4 studies identified a prolonged hospital stay related directly to the CL.

To our knowledge, no study compared treatment strategies for CL after pancreatic operation, although clinically relevant CL complicates up to 10% of pancreatic resections. Additional randomized studies comparing different treatment modalities are therefore unlikely. On a pathophysiologic basis, TPN may be very effective but is known to carry more procedure-related complications compared with dietary restrictions. Therefore, surgeons may prefer a step-up approach starting with dietary restrictions (a diet restricted in long-chain triglycerides or a no-fat diet with MCT supplementation); if

this dietary management does not lead to decreased drain output after a few days, TPN may be considered. Percutaneous catheter drainage of collections or chylous ascites is advised only in case of clinical symptoms. If TPN treatment fails, more invasive treatment options should be considered. Three strategies have been described: sclerotic (ie, lymphatic) embolization; a peritoneovenous shunt to decompress chyle from the peritoneum into the systemic circulation; and the use of lymphangiography to define the site of CL for operative ligation. However, data on these strategies are very limited, and success rates seem poor.^{14,27} Operative ligation of chyle leaks after an esophagectomy or mediastinal node dissection after pulmonary resection is both well described and very effective, but experience with operative management after pancreatectomy is very limited.^{31,32}

No evidence-based advice on the timing of removal of the drains can be given. In contrast, there also is no reported negative effect of early drain removal.^{33,34} Notably, drain removal after negative cultures combined with closure of past drain sites has been used as a treatment strategy by some ISGPS members.

Many studies have reported an association between the incidence of CL and the start of enteral feeding or the onset of a full oral diet, which is probably related to fat absorption from the diet (ie, long-chain triglyceride) increasing lymphatic flow and consequently increasing the volume and normalizing the color of the CL.^{14,21,25-27} However, early oral feeding after pancreatectomy is now well established as routine practice, and there is no evidence that withholding oral intake will decrease the development of CL itself.^{25,35-37}

Some studies have questioned the necessity of prophylactic intra-abdominal drainage after pancreatic resection.³⁸⁻⁴³ Abandoning intra-abdominal drainage excludes the possibility of early detection of CL in the drain output. In this case, suspicion of CL should be based on the clinical course of the patient and fluid collections seen on imaging and can be confirmed with percutaneous aspiration or drainage.

This consensus statement has limitations, which are essentially the consequence of the limited available data. Little information is available regarding confounding variables, which require investigation in the future. Also, prospective, large series regarding interventional treatment of CL are lacking but probably are not feasible because of the incidence of CL. In summary, CL is a clinically relevant complication after pancreatic operation that almost always responds well to nonoperative

measures. Considering the generally accepted and routinely used previous ISGPS definitions, the current consensus definition and grading system for CL after pancreatic operation should allow for valid assessment and comparison of complications after pancreatic operation.

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