Leakage of digestive juices from the pancreas with their unpredictable sequelae continues to pose a challenge to surgeons since Whipple’s addition of a pancreaticojejunostomy [1] to the classic Kausch-Whipple pancreaticoduodenectomy in 1942 [2,3]. Although the mortality associated with pancreaticoduodenectomy has been dramatically reduced over the past 70 years (from 20% to <3%), morbidity rates have remained stubbornly constant at approximately 40% [4–14]. Although the list of complications associated with a Whipple operation is substantial, an uncontrolled pancreatic leak and its associated downstream effectors of sepsis, hemorrhage, and multiorgan failure remain the most dramatic and lethal. Although the mortality rates associated with a pancreatic leak have been substantially reduced by the application of modern critical care, nutritional support and percutaneous catheter drainage techniques, systemic sepsis, and visceral pseudoaneurysms still occur, and when present, result in mortality rates of up to 40% [11,15–19]. Efforts to reduce the 10% to 25% incidence of pancreatic-enteric anastomotic leaks have invigorated surgeons to explore innovative technical modifications to this portion of the operation [7,15,16,20]. More than 1700 publications commenting on pancreatic anastomosis have been listed in PubMed over the past 50 years chronicling the employment of different reconstructive organs, sewing techniques, pancreatic duct stenting methods, pharmacologic manipulation of pancreatic secretion, application of topical adhesives, and methods of external drainage [21]. Whenever one encounters a body of literature this extensive that focuses on one technical aspect of an operation, it generally means: (1) it is viewed as an important problem by surgeons, and (2) no adequate solution to the problem exists.

As alluded to in the preceding discussion, there remains a paucity of rigorously designed large multi-institutional randomized controlled trials (RCT).
to allow one to draw definitive conclusions regarding the optimal technique to use to reduce the pancreatic leak rate following Whipple operation. Although several valid attempts at achieving level I data have been completed, including several moderately large, randomized multi-institutional clinical trials [22–24], much of our current understanding, or lack thereof, is predicated on single-surgeon case series reports. Although it is true that these reports have been authored by many of the true giants in pancreatic surgery, single-surgeon case series remain prone to significant biases, including volume-outcome covariates, learning curves issues, and difficult to transfer knowledge and skill sets. Furthermore, case series reporting poor outcomes using a new or modified technique are rarely published, providing a substantial publication bias in favor of positive studies. The importance of surgeon experience on the postoperative rate of pancreatic leakage is perhaps the most important factor in this challenging technical exercise [6,21,25–28]. Although this particular variable has proven nearly impossible to accurately quantify, it remains a significant covariate in all studies. As a result of this confounding factor, regardless of country or center, high-volume surgeons at busy centers who are able to master a given technique through frequent repetition have better outcomes and lower pancreatic leak rates than surgeons who do not have these characteristics [21]. In addition to these single-surgeon case series, a large number of studies have been done using a retrospective cohort design that limits our ability to draw definitive conclusions. Issues, such as selection bias, temporal bias (began with technique x and then switched to technique y with improved results), confirmation bias, and poor outcome definitions are some of the troubling methodological limitations in this body of literature. Analogous to single-surgeon case series, these studies rarely control for surgeon experience and are often influenced by variables other than the direct technical factors of interest (anastomotic technique) by not controlling for concomitant stent placement, octreotide treatment, or sealant use. It seems to be an infrequent occurrence for surgeons to limit their technical modifications to a single, well-defined measureable variable. This observation is exemplified in a recent report finding fewer pancreatic leaks using a three-stage procedure incorporating a pancreaticogastrostomy, external continuous suction drainage of pancreatic juice, wrapping the pancreatic anastomosis with the round ligament, and applying fibrin glue sealant [29,30]. Which specific factor contributed to the improved results they cite is of course, a matter of speculation, not science. Although conclusions drawn from an RCT in theory are more transferable, variability in definitions, patient populations, clinical endpoints, and individual surgeon’s skill sets significantly limits broad generalizations when applied to technique-based investigations. Nevertheless, it is only through carefully designed, large, multi-institutional RCTs do we have any true hope of eliminating the nearly ubiquitous statement, “future randomized studies are required,” found at the conclusion of most papers on this topic. Given these significant limitations, this article reviews the recent literature pertaining to the technical approaches designed to reduce pancreatic leaks following a Whipple operation.
DEFINITIONS
Consistent and reliable terminology has not been applied in the literature with regard to pancreatic leaks following a Whipple operation. As a result of this inconsistency, heterogeneous definitions of pancreatic leaks and fistulae, as well as their clinic sequelae, abound [20]. This article defines a pancreatic fistula as an abnormal communication between two epithelialized structures. Leak or leakage is defined as an abnormal escape of fluid from the pancreas gland itself [25]. Because these terms have been used interchangeably within the literature, as well as the fact that amylase-rich pancreatic juice may drain from either the pancreatico-enteric anastomosis or the transected surface of the gland, both terms are included in this article. This inclusiveness is clearly evident in the International Study Group for Pancreatic Fistula (ISGPF) lexicon, which defines a pancreatic fistula in the broadest sense by including all peripancreatic fluid collections, abscesses, leaks, and fistulas thought to originate from either the anastomosis or pancreatic gland surface: “any measurable volume of fluid on or after postoperative day three, with an amylase content greater than three times the upper limit of normal serum” [20]. Until the recent adoption of a common lexicon and grading system by the ISGPF it was nearly impossible to compare the results from different published series or centers in any meaningful manner.

UNMODIFIABLE ANASTOMOTIC RISK FACTORS
Unmodifiable risk factors associated with the occurrence of a pancreatic leak following a Whipple operation include a laundry list of anatomic and physiologic factors: patient age (>70 years), sex (male), jaundice (duration), coronary artery disease, hemoglobin A1c level (diabetes mellitus), creatinine clearance (<50 mL/min), periampullary neoplasms besides pancreatic cancer (duodenum, terminal bile duct, ampulla of Vater), blood supply to the pancreatic remnant, and the volume of pancreatic juice output [17,31–45]. These variables are, for the most part, related to the general capacity for wound healing and not necessarily specific to a pancreatic anastomosis. Although the specific impact of each of these factors can be debated, the direct consequences of pancreatic gland texture and duct size have been repeatedly highlighted over decades of publications. The higher pancreatic leak rate associated with a soft, fatty, non-fibrotic gland with a small (<4 mm) pancreatic duct is clear to even the most junior pancreatic surgeon [6,21,25,26,45]. It appears that a soft pancreas conveys up to a 10-fold increased risk of subsequent pancreatic leak/fistula [17,31,40,45–50] and this risk appears to be independent of the specific type of pancreatico-enteric anastomosis constructed [22]. These same observations of a higher pancreatic leak rate have consistently been made for the presence of a small pancreatic duct [17,38,45]. Ducts less than 4 mm in diameter are particularly problematic and may confer a greater than 3-fold increased risk of subsequent fistula [17,38]. Magnification of the surgical field using a microscope during pancreaticojejunostomy has been proposed in this setting as a useful adjunct [51]. These risk factors coexist with potentially modifiable
factors, such as operative time, excessive intraoperative blood loss (>1500 mL), use of neoadjuvant chemoradiotherapy (protective), and type of anastomosis constructed. The remainder of this article focuses on the technical factors of pancreatic-enteric reconstruction that have been associated with a reduced leak rate following Whipple operation.

TECHNICAL FACTORS

Reconstructive organ

Debate over the best reconstructive organ (stomach vs jejunum) for restoration of pancreatic-enteric continuity can be traced to the initial description of pancreaticogastrostomy by Waugh and Claggett in 1946 [52]. Anastomosing the pancreatic remnant to the posterior stomach has several plausible advantages that include: (1) a rich gastric wall blood supply to improve anastomotic healing, (2) a tension-free anastomosis caused by the close proximity of the stomach to the pancreatic remnant, (3) avoidance of a long traction-prone jejunal loop, and (4) inactivation of troublesome digestive pancreatic enzymes (trypsin) by gastric acid secretion (Fig. 1). Similarly, jejunum also has several theoretical advantages as a reconstructive conduit including: (1) ease of approximation because of the mobility of the jejunal mesentery, and (2) a rich jejunal blood supply for anastomotic healing. A recent single-institution randomized clinical trial compared 53 subjects with gastric partition pancreaticogastrostomy to 55 subjects with conventional pancreaticojejunostomy where they reported a lower pancreatic leak rate (4% vs 18%, \( P < .01 \)) using pancreaticogastrostomy [53]. These investigators speculate that although pancreatic juice continues to drain directly into the stomach using this technique, benefits are derived from the anastomosis resting outside the flow of gastric contents into the jejunum (Fig. 2). One concern in the design of this study is that both anastomoses were done using short (6 cm) silastic internal pancreatic stents, an uncontrolled variable that may have influenced their results.

Many authors have attempted to delineate which of these two procedures is superior [8,29,53–69] and 4 prospective randomized clinical trials comparing pancreaticogastrostomy to pancreaticojejunostomy have been completed [23,38,70,71]. Despite variable definitions of end points and incidences (0% to 14%) of pancreatic leak/fistula rates between trials, no significant differences between these two techniques were identified. Further evidence of this clinical equipoise is found in a recent meta-analysis that concluded that the two techniques of anastomosis were not different in terms of pancreatic fistula rate or overall postoperative morbidity rates [66]. Despite the equivalence of these two techniques in the early postoperative period, troubling long-term functional deficits, including both anastomotic stenosis and pancreatic endocrine insufficiency, have been reported with pancreaticogastrostomy [72–75]. To date, jejunum remains the favored conduit for pancreatic enteric anastomosis and its use has provided surgeons with a consistent and predictable pancreatic leak rate in the 2% to 19% range [76]. Use of the stomach for reconstruction remains firmly entrenched in the practice of several high-volume surgical
groups who continue to advocate its benefits [57–61]. Taken as a whole, studies of the best methodologic quality indicate that anastomosis of the pancreatic remnant to either the jejunum or stomach is an equivalent technique with regard to the incidence of major morbidity and postoperative pancreatic leak rates.

Fig. 1. Technique of pancreaticogastrostomy. (A) After mobilization of at least 4 to 6 cm of the pancreas from the splenic artery and vein, a posterior layer of 3-0 silk sutures are placed through the anterior capsule of the pancreas 2 cm from the transaction margin into the seromuscular layer on the left lateral aspect of the size-matched gastrostomy. The gastrostomy is located on the posterior wall of the stomach. Note the clockwise rotation of the stomach around its axis to facilitate this retrogastric reconstruction. (B) While the stomach is still rotated, after completing the posterior layer of the anastomosis, the pancreatic remnant is invaginated into the stomach and the anastomosis is completed by an anterior row of 3-0 silk sutures placed 2 cm back from the cut end of the pancreas. Note the mobility required of the remnant pancreas off the splenic artery and vein to facilitate this anastomosis. (C) Counterclockwise rotation of the stomach returns it to its normal anatomic configuration and the subsequent pyloroejunostomy is completed. Note the position of the posteriorly placed invaginated pancreaticogastrostomy as seen through the stomach in this drawing.
Technique of pancreaticojejunostomy
Although the specific technical modifications of pancreaticojejunostomy described in the literature are detailed and varied, these numerous contributions can be broken down into 3 common variants: (1) end-to-side duct-to-mucosa (Fig. 3A); (2) end-to-side invagination (see Fig. 3B); and (3) end-to-end invagination (see Fig. 3C). In an end-to-side duct-to-mucosa anastomosis, the pancreatic duct is sewn directly to the jejunal mucosa in either an interrupted or running manner using a fine monofilament absorbable suture. Invagination techniques incorporate both the pancreatic duct with varying portions of the pancreatic parenchyma sewn to the full thickness of jejunum in either an end-to-end or end-to-side configuration of the cut end of the pancreas to the jejunum. Although these techniques vary in specifics, they do share common principles including a secure, tension-free anastomosis; adequate blood supply; and pancreatic juice draining directly into the gastrointestinal tract near the biliary anastomosis [26]. The search for the optimal pancreaticojejunostomy has also led to several independent and original suggestions. Most notable are the binding pancreaticojejunostomy described by Peng using mucosal ablation and end-to-end invagination [77–79], a trans-pancreatic U-stitch technique that aims to reduce shear forces during knot

Fig. 2. Gastric partition pancreaticogastrostomy. In this variant, the anastomosis of the pancreas to the stomach is constructed outside the flow of gastric contents into the duodenum by use of a gastric partition staple line. In this technique as described, the anastomosis is constructed using a short (6 cm) internalized pancreatic duct stent (see Fig. 5).
tying [80,81], and modified invagination techniques [82,83]. Despite several nonrandomized and randomized trials [77,84–87], no single investigation has been able to definitively confirm the advantage of one technique over another in reducing the risk of subsequent pancreatic leaks. This clinical equipoise also extends to numerous cohort studies [83,88–94], and appears to be independent of the suggestion that invagination techniques may be superior in patients with soft pancreatic remnants and small pancreatic ducts [38]. With regard to this later point, in a randomized trial of 144 subjects with predominantly soft glands (90%), no benefit was observed in the pancreatic leak rate for either technique [87]. Retrospective studies imply that employing a continuous duct-to-mucosa anastomosis reduces subsequent leaks when compared with an interrupted technique [94,95]. Although a few studies reported superiority of the duct-to-mucosa technique over various invagination approaches [31,42,84], a recent, large, prospective dual-institution trial of 197 subjects reported exactly the opposite conclusion identifying significantly fewer 

Fig. 3. Common types of pancreaticojejunostomy. (A) End-to-side duct to mucosal pancreaticojejunostomy. (B) End-to-side invaginated pancreaticojejunostomy. (C) End-to-end invaginated pancreaticojejunostomy (with internal transanastomotic stent).
pancreatic fistulas (12% vs 24%, \( P < .05 \)) in the end-to-side invagination cohort [22]. These investigators again highlighted the importance of soft gland texture and small duct size as perhaps the main determining factors in the development of pancreatic leaks. Despite this well-done RCT, judgments based on the totality of the current surgical literature support that duct-to-mucosa and invagination techniques remain equivalent with regard to the incidence of postoperative pancreatic leaks.

Separate jejunal limb
Irrespective of the particular type of pancreaticojejunostomy, some surgeons advocate the use of a dedicated jejunal limb for this anastomosis (Fig. 4). In theory, this technique limits the activation of pancreatic juice enzymes by isolating them from the biliary effluent, which travels through a separate parallel limb in this method of reconstruction. Unfortunately, although some investigators have reported lower rates of pancreatic fistula in small personal series [96–105], neither a recent small retrospective series [106] nor 2 prospective nonrandomized trials [107,108] comparing an isolated Roux loop

![Fig. 4](image-url) 

**Fig. 4.** Separate jejunal limb pancreaticojejunostomy. In this reconstruction, similar to the gastric partition pancreaticogastrostomy (see Fig. 2), this technique theoretically isolates the pancreaticojejunostomy outside of the normal digestive stream limiting pancreatic enzyme activation at the anastomosis. The pancreaticojejunostomy can be constructed end-to-end (as shown) or end-to-side (duct-to-mucosa or invaginated) and the length of the isolated limb of jejunum can be shortened (20 cm) or elongated (40 cm) depending on the requirements for each individual patient.
Pancreaticojejunostomy versus a standard pancreaticojejunostomy have identified a benefit in terms of postoperative pancreatic leaks.

Pancreatic duct stenting
The use of transanastomotic stents has several theoretical advantages: (1) diversion of pancreatic juice away from a fresh pancreatico-enteric anastomosis, and (2) protection of the pancreatic duct during suture placement. Potential downside risks include stent migration and pancreatic duct obstruction. As with the previous discussion of technical modifications, although good evidence exists to support the use of transanastomotic stents, a definitive conclusion based on irrefutable level 1 evidence remains lacking.

Internal transanastomotic stenting uses a short (6 cm) silastic stent placed across the pancreaticojejunostomy anastomosis (3 cm into the pancreas and 3 cm into the jejunum) which terminates intraluminally within the jejunal limb or stomach (Fig. 5). External transanastomotic stenting involves delivering a long silastic stent (eg, 5-F pediatric feeding tube) traversing through both the bowel and anterior abdominal wall to allow for complete external drainage and diversion (Fig. 6). Although a recent RCT advocating externalized...
transanastomotic stents attached to a closed suction drainage device reported a reduction in the incidence of postoperative pancreatic fistulas [109], most pancreatic surgeons use gravity drainage only for these stents. Potential advantages of an externalized stent include: (1) a more complete diversion of pancreatic juice away from the anastomosis, and (2) prevention of biliary activation of the pancreatic zymogens. Comparisons of these two techniques are common within the literature, as are studies evaluating the necessity of the stents themselves [24,110–119]. Although cohort studies have indicated that internal stenting may reduce the risk of pancreatic fistula [110,111], subsequent prospective studies in both soft, normal pancreatic glands [112] and in those subjects reconstructed with an isolated jejunal limb [113], or via standard pancreaticojejunos-tomy [114], found no differences in either the frequency or severity of pancreatic leaks. Although external pancreatic stenting has been associated with a low (0.0% to 4.2%) incidence of pancreatic fistula in several personal series [115–117], it has also been compared with no stenting in multiple study designs. A recent retrospective review failed to identify any advantage to an external transanastomotic stent with regard to pancreatic leak rates [118]. A nonrandomized study of 85 subjects, however, identified a decreased incidence of postoperative pancreatic leaks [119]. In a well-designed RCT of 120 subjects

Fig. 6. Long, external transanastomotic pancreatico-enteric stenting. In this technique, a full-length pediatric feeding tube (5 or 8 French in size, matched to the internal diameter of the pancreatic duct) is brought into the jejunum via a Witzel-tunnel technique and placed across the pancreaticojejunostomy during construction. The tube after leaving the biliopancreatic limb via the Witzel tunnel is then brought out through the anterior abdominal wall serving as a controlled pancreatic fistula until healing of the anastomosis, after which it can be removed in the outpatient clinic.
by Poon and colleagues, fewer pancreatic leaks (6.7% vs 2.0%) were found in the subject cohort that used external pancreatic duct stents versus the control group with no stenting. This trial is to be applauded for a tight methodology, including analyzing one specific variable while carefully standardizing the technique of pancreaticojejunostomy (duct-to-mucosa) used [24].

Surprisingly, given the previously mentioned information on the overall utility of pancreatic duct stenting in general, both nonrandomized [120] and randomized [121] prospective clinical trials comparing internal pancreatic stents to external transanastomotic stenting have found no significant benefit to one technique over the other with respect to rate of subsequent pancreatic leaks. A recent publication has reported an increase in the incidence of delayed gastric emptying with the use of pancreatic duct stenting when compared with avoiding stents all together [122]. Taken as a collective, the literature surrounding the use of pancreatic stents remains curious because of its lack of internal inconsistency. Although studies evaluating external transanastomotic pancreatic stents generally support their use, those evaluating internal pancreatic stents have consistently shown no benefit. Oddly, when direct comparisons are made between internal and external stenting, rather than identifying a benefit with external stenting as one would expect based on the individual data, no significant advantage is identified between groups. As a result of these inconsistencies, it remains uncertain if placement of a stent (either internal or external) significantly reduces the rate of postoperative pancreatic fistulas/leaks during pancreaticojejunostomy.

Prophylactic anastomotic drainage
External drainage of pancreatic-enteric anastomosis via either open or closed-suction drainage techniques have a long impassioned history. Although the current trend in general surgery is to minimize their use in a wide variety of complex operations (hepatic, colon, rectal, appendectomy) [123,124], external drainage has remained a fixture in pancreatic surgery. Closed suction drains are classically placed around the pancreatic anastomosis to control a pancreatic leak should one occur, with the hope of transforming an anastomotic leak into a controlled pancreatic fistula thereby avoiding the potential morbid consequences. Without adequate control of a leak (drainage by either a surgeon or interventional radiologist), patients may progress to the development of systemic sepsis, multiorgan failure, and potentially death. Further confounding these unyielding notions is the rather distinct possibility that routine intraperitoneal pancreatic drainage may actually generate leaks from the anastomosis following pancreateoduodenectomy. This leak-generating potential is particularly plausible for closed-suction drainage systems where the suction bulb generates a significant negative pressure to the area surrounding the anastomosis [125,126]. Although this pressure decreases with liquid filling of the reservoir, it can be substantially increased with stripping of a drain (−175 mm Hg), data that have led some surgeons to place their intraperitoneal closed-suction drains to gravity. Because of the high risk associated with not adequately controlling a pancreatic fistula, pancreatic surgeons have been
slow to incorporate the results of both a retrospective review [127] and a RCT of 139 subjects to either intraperitoneal drainage or no drainage following pancreatectomy [128]. In this study, Conlon and colleagues found no significant differences in either the number or type of complications, the need for subsequent interventional radiologic drainage or reoperation, or the overall mortality rate between the two subject groups. Although this study has been criticized for several methodological flaws, these compelling findings mandate an appropriately powered, multi-institutional study to carefully examine these issues because the current use of routine intraperitoneal drainage following pancreateicojejunostomy is not based on sound scientific evidence.

In addition to placing the drain, the length of time that a peripancreatic drain is left in place is an additional factor associated with the risk of subsequent pancreatic leaks. Similar to the arguments surrounding routine placement of intraperitoneal drains, this variable is embroiled with a long history of art and tradition. Although some pancreatic surgeons remove drains early based on low drain amylase values, others maintain peripancreatic drainage until the patients are tolerating a regular diet to ensure that a pancreatic fistula is not present with full pancreatic stimulation. A recent RCT has addressed this issue by concluding that fistula rates are lower if the drain is removed on postoperative day 3 provided the drain amylase level is below 5000 IU/L [129]. A link between early drain removal after pancreateoduodenectomy and fewer pancreatic leaks may also be relevant given the observation of a lower institutional pancreatic fistula rate with a generally more rapid drain removal protocol at one institution in the RCT of invagination versus duct-to-mucosal anastomotic techniques [22].

**SUMMARY**

Despite the overwhelming limitations that plague the literature surrounding the optimal method of reestablishing pancreatoco-enteric continuity following a Whipple operation, it is clear that all successful techniques conform to sound surgical principles. These principles include a water-tight and tension-free anastomosis, preservation of adequate blood supply for both organs involved in the anastomosis, and minimal trauma to the pancreas gland. Although surgeon experience, gland texture, and pancreatic duct size are clearly the dominate risk factors from a long list of variables associated with pancreatic leaks following pancreateoduodenectomy, these are nonmodifiable covariates. Although the plethora of current literature cannot provide a single definitive technical solution for restoring pancreatoco-enteric continuity, a small number of well-designed RCTs [22,24] support the use of transanastomotic external stenting for high-risk pancreatic glands and an end-to-side invaginated pancreatocojejunostomy. The truth remains that an individual surgeon’s mastery of a specific anastomotic technique, in conjunction with a large personal experience, is likely to be the best predictor of a low pancreas leak rate following pancreateoduodenectomy.
References


