Abdominal Pain Following Total Pancreatectomy With Islet Autotransplantation

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Objective: Total pancreatectomy with islet autotransplantation (TPIAT) is increasingly used as an option for the treatment of chronic and recurrent acute pancreatitis in selected patients. Studies have shown significant improvements in pain, quality of life, and opioid use postoperatively. However, in long-term follow-up, over half of the patients have episodes of abdominal pain following TPIAT. The aim of this work is to describe the array of causes of abdominal pain in this complex and growing patient population.

Methods: We conducted multidisciplinary discussions with experts at our institution and reviewed literature, where available, to identify and describe the diverse causes of abdominal pain following TPIAT.

Results: We identify 15 distinct causes of abdominal pain following TPIAT, describing their presentation, workup, and management.

Conclusion: As more patients undergo TPIAT, we must plan for and address the associated causes of abdominal pain that result from alterations in anatomy and physiology, both in the short and long term.

Key Words: total pancreatectomy with islet autotransplantation, abdominal pain, postoperative

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Total pancreatectomy with islet autotransplantation (TPIAT) is increasingly utilized for the treatment of chronic and recurrent acute pancreatitis when other medical, endoscopic, and/or surgical treatments have failed. The primary objective of TPIAT is to improve the quality of life for patients who suffer from debilitating abdominal pain secondary to these disorders. Pain, quality of life, and opioid dependence improve for most patients following TPIAT.[1] While once considered to be a rare procedure performed only at specialty centers, the number of centers performing TPIAT and the total number of patients undergoing the surgery has been increasing in recent years.[2] Patients undergoing TPIAT require long-term health maintenance. One of the more common and often challenging postoperative symptoms to treat is the recurrence of abdominal pain of unclear cause, with very little guidance on this topic in the medical literature. Based on our center's experience, we summarize both common and rare causes of recurrent pain following TPIAT and an algorithm to guide evaluation in these cases.

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BACKGROUND

Constant or recurrent abdominal pain is the hallmark of chronic pancreatitis, present in 80%–90% of patients who suffer from this disease.[3] While the pathophysiology of pain in chronic pancreatitis is not completely understood, it appears to be multifactorial with evidence for mechanical causes, neurological changes within the pancreas, and changes in central and peripheral pain processing.[4–8] Current guidelines regarding chronic pancreatitis emphasize the benefit of early surgical intervention to achieve optimal long-term pain relief before the development of more advanced stages of disease.[9] In the appropriately selected candidate, this may include TPIAT.

The rationale behind TPIAT is to remove the nidus of pain, while retaining some degree of islet cell function for blood glucose homeostasis. Key aspects of the surgery include total removal of the pancreas and typically the spleen, followed by variable reconstructive techniques of the gastrointestinal tract, shown in Figure 1. Roux-en-Y reconstruction is often the preferred choice in current practice, while historically, single-limb loop reconstruction was also common.[10] Islet cells are harvested at the time of surgery and transplanted into the liver via the portal vein. A gastrojejunostomy tube is placed for postoperative feeding and gastric decompression.

TPIAT is inherently trading one disease state for another. With the removal of the entire pancreas, the nidus of chronic pancreatic abdominal pain is gone. All patients undergoing TPIAT have complete exocrine pancreatic insufficiency postoperatively. In addition, endocrine pancreatic function is curtailed, with islet autotransplantation successful to varying degrees.

At our institution, patients report improved pain at rates of 77.1% at 1 year, 75% at 5 years, and 81.5% at 10 years following TPIAT.[1] However, it is also notable that over 60% of patients report abdominal pain of any cause at 1–10 years post-TPIAT.[1] As this is typically an operation performed for benign pathology, patients have excellent long-term survival.[11] Despite the growing number of

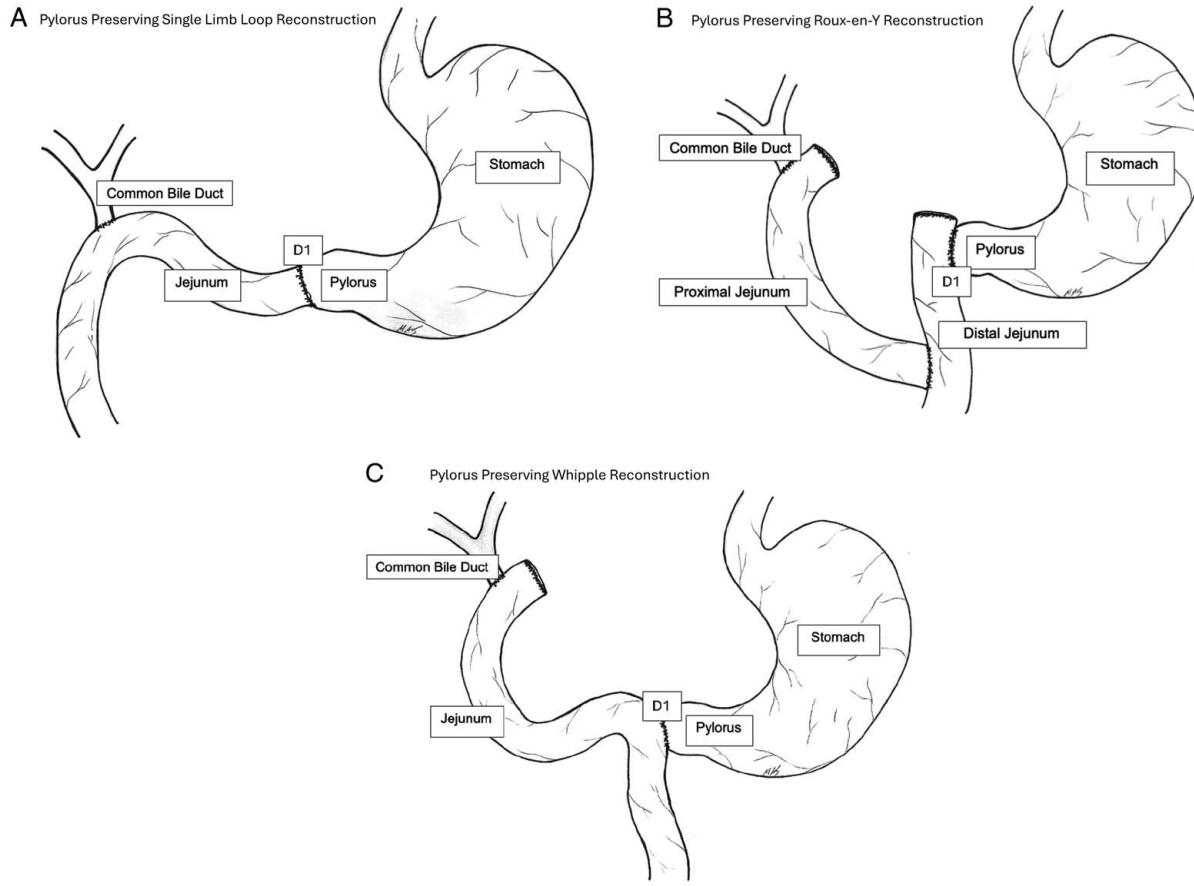

FIGURE 1. Various reconstruction options of the gastrointestinal tract following TPIAT. A–C, Show various reconstructive options of the gastrointestinal tract with pylorus preservation, following total removal of the pancreas. Each of these may also be completed with removal of the pylorus.

patients living post-TPIAT, knowledge of medical and surgical challenges following this surgery remains limited.

METHODS

This is an integrative review informed by institutional experience at a high-volume TPIAT center and a targeted review of the literature. Our objective was to identify and describe potential causes of recurrent abdominal pain in the post-TPIAT population. Causes of abdominal pain were identified through a multidisciplinary, iterative process involving surgeons, gastroenterologists, endocrinologists, and nurses who care for both adult and pediatric TPIAT patients at our institution. To supplement our clinical insights, we conducted a focused literature search in PubMed on topics relevant to TPIAT, including chronic pancreatitis, postoperative pain, complications, specific causes of abdominal pain, and approaches to pain management. Articles were included based on relevance to post-TPIAT pain. Data from analogous populations (patients undergoing Whipple procedures) were included when applicable, with explicit acknowledgment of extrapolation.

This manuscript reflects a synthesis of published findings where available, supported by expert opinion derived from our experience managing a large cohort of TPIAT patients. The following sections outline the spectrum of abdominal pain etiologies observed in our TPIAT population, accompanied by a discussion of underlying pathophysiology and corresponding clinical management strategies. Given that certain causes of abdominal pain following TPIAT are influenced by the type of surgical reconstruction performed, Figure 1 illustrates the various reconstructive techniques often performed.

CAUSES OF ABDOMINAL PAIN FOLLOWING TPIAT

The differential of abdominal pain following TPIAT is broad and varies depending on the length of preoperative pain and the amount of time lapsed since the procedure. The evaluation requires knowledge of common causes of abdominal pain, as well as chronic pancreatitis-associated pain and TPIAT. Complications of exocrine or endocrine pancreatic insufficiency may also contribute to pain after TPIAT. Anatomic, hormonal, and innervation changes post-TPIAT all contribute to altered gastrointestinal physiology.

Table 1 displays common causes of abdominal pain following TPIAT in relation to postoperative timing. In the text below, we describe some of these causes. This list is not exhaustive. It is often the case that more than one etiology of pain is present concurrently, and that patients will require multiple treatment modalities.

TABLE 1. Causes of Abdominal Pain Following TPIAT

	Early 0–14 d	Middle 14–90 d	Late > 90 d
Opioid related	Inadequate dosing perioperatively	Weaning process	Chronic pain Opioid induced hyperalgesia
Incisional pain	Expected postoperative	Prolonged Tethering at G tube site	Chronic
Gastroparesis	Preexisting Expected postoperative finding	Prolonged recovery of gastric motility	Chronic changes to gastric motility Autonomic neuropathy (> 5 y) Enteroendocrine axis disturbances Opioids
GI dysmotility	Postoperative ileus	Obstipation	Obstipation Neuronal changes Adhesive Disease
Infection	Surgical site infection Abscess Anastomotic leak	Deep space infection Cholangitis	Cholangitis
Mechanical causes	Technical complication causing obstruction	Internal hernia Closed loop obstruction Afferent limb syndrome	Internal hernia Closed loop obstruction Afferent limb syndrome Adhesive disease
Gut microbiome related	Peri-operative antibiotics	Small intestinal bacterial overgrowth	Small intestinal bacterial overgrowth
Malabsorption related	Inadequate pancreatic enzyme supplementation	Inadequate pancreatic enzyme supplementation Vitamin deficiencies	Inadequate pancreatic enzyme supplementation Vitamin deficiencies Nephrolithiasis
Other causes		Marginal ulceration Alkaline gastritis	Marginal ulceration Alkaline gastritis

Opioid Dependence and Withdrawal

A significant number of TPIAT patients (nearly all adults and some children) are opioid dependent preoperatively. Postoperatively, patients receive their baseline requirement plus appropriate additional pain control as they have undergone a major abdominal operation. We utilize multimodal pain control as much as possible, including perioperative paravertebral catheters for local anesthetic delivery and dexmedetomidine and ketamine adjuncts, and an intravenous narcotic regimen that includes both continuous and intermittent narcotic (typically hydromorphone) delivered using a patient-controlled analgesia (PCA) device. Narcotic dose is titrated to patient comfort. All patients are started on gabapentin at the time of surgery.

At 5–7 days postoperatively, dexmedetomidine and ketamine adjuncts are weaned, and a regimen of long-acting enteral narcotic at 75% of the daily intravenous dose (typically methadone) is initiated, with gradual transition off of patient-controlled analgesia (PCA) narcotics. Intermittent enteral narcotics are utilized for additional pain control. We do not begin to wean opioid dosing until several weeks postoperatively, in the outpatient setting, after acute postoperative pain has resolved. We begin weaning intermittent narcotics first, followed by gradual methadone weaning (this will frequently take some months). Gabapentin is continued until the narcotic wean has been completed.

Even with these measures, opioid withdrawal symptoms can contribute to ongoing abdominal pain following TPIAT. In the immediate postoperative period, this can be due to inadequate dosing. Typical postoperative opioid management in these patients includes long-acting and short-acting opioids. We wean short-acting opioids first, followed by a slow taper of long-acting opioids, usually no more frequently than every 2 weeks. It is important to counsel the patient and family about the symptoms of opioid withdrawal, including anxiety, nausea, vomiting, and abdominal pain, and to reassure them that these symptoms are typically short-lived and self-limited. We routinely engage pain specialists to assist with opioid weaning.

There are no guidelines for the management of neuropathic pain in patients after total pancreatectomy with islet autotransplantation. It is frequently difficult to distinguish neuropathic pain from pain of other causes. There are active investigations ongoing exploring biomarkers in related populations of patients.[6] In addition to the use of gabapentinoids, a variety of other pharmacologic agents can be utilized.[12] Nonpharmacologic treatments include physical therapy, including therapeutic ultrasound and psychotherapy.

Incisional Pain

Incisional pain is to be expected in the immediate postoperative period. Patients undergoing TPIAT are likely at increased risk of severe incisional pain, as both the presence of pain before surgery and the severity and duration of acute postoperative pain are predictors of chronic pain postsurgery.[13,14] This is an additional reason for aggressive immediate postoperative management of pain, with utilization of regional anesthesia and delayed weaning of opioids.

In some patients, incisional pain crosses the threshold from expected to recurrent or chronic. This occurs weeks to months postsurgery. Recurrent incisional pain most often presents as pain with exertion, stretching or pulling at the incision site, or focal tenderness with increased abdominal distention, such as after a meal. Treatment strategies include physical therapy, trigger point injections, and daily light exercise such as walking.[15] Occasionally, the pain is localized to the site of the gastrostomy tube, in which case a local anesthetic injection at the site can be both diagnostic

and therapeutic. In these patients, revision of the gastrostomy tube site may be beneficial. Recurrent incisional pain can also present with neuropathic features, such as burning, stabbing, or shooting sensations occurring without a clear trigger. We treat these symptoms with neuropathic pain modulators such as gabapentin or pregabalin.

Abscess

Abscess or deep surgical site infection often present with a recurrence of abdominal pain after initial improvement. This is typically in the timeframe of a week to a couple of months postsurgery. Symptoms can also be nonspecific or masked by postoperative analgesia. TPIAT is considered to be a clean-contaminated case, although its long duration increases the risk of postoperative infection.[16] Recent data from the POST trial shows a 12% rate of infectious complications requiring some form of drainage procedure in the adult cohort.[10]

Drain placement can be complicated by the patient's altered anatomy. In extreme cases, a reoperation may be necessary.

Abscess should be distinguished from postoperative fluid collection. Data on the relationship between postoperative fluid collections and their relationship to pain, specifically in TPIAT patients, does not exist. Extrapolating from post-Whipple patients, one could expect around half of the patients to have transient postoperative fluid collections on imaging.[17] These collections can be distinguished from abscess via radiographic differences on CT or MRI as well as clinical signs.[18] Intervention, such as image-guided or endoscopic drainage, is generally reserved for collections that become symptomatic or infected.

Obstipation

Obstipation is one of the most common causes of abdominal pain postoperatively, and can present as an acute postoperative issue or become chronic or recurrent months to years after TPIAT. There are physiological changes associated with loss of the pancreas and duodenum, changes induced in bowel motility from narcotics, and presumed changes in bowel function long term.[19–22] Obstipation is especially common in those treated with opioids for a prolonged period of time.

Many patients will have diffuse or localized abdominal pain associated with food intake, sometimes made better or worse with defecation. Patients may or may not describe low stool output, straining, or hard stools. Impaction of stool can cause overflow diarrhea. Plain film abdominal x-ray or CT scan will show a large stool burden, although it is important for the clinical team to review the images, as many radiologists do not routinely comment on this.

In our experience, it typically takes up to 1 year for most patients to adapt to the physiological changes following TPIAT and achieve a stable baseline in bowel function. During this time, pancreatic enzyme replacement therapy is often adjusted. This center does nutrition monitoring every month for the first year, then annually for as long as patients follow up. This includes visceral protein stores, fat-soluble vitamin levels, iron stores, and fatty acid levels.

When obstipation is encountered, we initiate therapy using a standard cleanout protocol, followed by an osmotic and stimulant laxative regimen. It is important to emphasize the development of good bowel habits, such as adequate hydration and fiber intake, and routine medications to promote colonic motility. Treatment is often a months-long process if patients remain on chronic opioids. In addition, pancreatic enzyme replacement therapy should be adjusted to regulate bowel movements, balanced with nutritional monitoring. In patients with recurrent symptoms of obstipation it may be worthwhile to consider prokinetic agents such as linaclotide.

Cholangitis

Cholangitis is a known risk of biliary reconstructive surgery, including TPIAT.[23,24] Data is limited as to the relationship between reconstructive technique and risk of cholangitis. There are several mechanisms by which cholangitis occurs. Obstructive cholangitis, such as caused by stricture at the site of the biliary anastomosis or elsewhere in the biliary tract, has been reported from a few months up to a decade postsurgery.[23] Cholangitis can also occur without obstruction; in these cases, biliary reflux is a hypothesized cause. Resection of the sphincter of Oddi results in the loss of its protective function of closing the biliary tract to reflux of enteric contents, including bacteria. At our institution, patients with nonobstructive cholangitis may present years after TPIAT, sometimes in a recurrent fashion. Possible etiologies include a short biliary limb or intermittent obstruction in the downstream bowel at the jejunojejunostomy, promoting reflux of intestinal contents.

For patients presenting with abdominal pain, fever, and liver function test abnormalities, cholangitis must be on the differential. Typically, workup consists of a right upper quadrant ultrasound, CT scan, and possibly an MRCP. If there is evidence of obstruction, such as dilated ducts, further workup and treatment via ERCP or interventional radiological approaches are indicated. Very occasionally, reoperation is required for persistent or recurrent biliary stricture. In cases without obstruction, treatment of cholangitis consists of antibiotic therapy. Long term, prevention of recurrence is often more challenging. One recent case report highlights the success of fecal microbiota transplantation in the treatment of recurrent nonobstructive cholangitis years after TPIAT, highlighting the possible role of dysbiosis in this condition.[25]

Special consideration should be given to internal biliary stents and their potential role in the development of cholangitis. Internal biliary stents are occasionally utilized during reconstruction in patients undergoing pancreatic resection involving the duodenum and distal common bile duct (CBD). If retained, these stents can lead to long-term complications, including stent occlusion, biliary stasis, and recurrent cholangitis. It is important to review operative records from the index procedure to determine whether a biliary stent was placed. In addition, appropriate imaging—such as MRCP or CT—should be reviewed to assess for the presence of a retained stent.

If a retained stent is identified in the setting of cholangitis, endoscopic removal should be pursued. However, retrieval may be technically challenging depending on the reconstructive anatomy. A dilated CBD, typically defined as >0.5 cm in diameter, may further support suspicion for biliary obstruction in this context.

Gastroparesis

Gastroparesis represents a common cause of pain postoperatively in TPIAT patients.

This can be viewed as a spectrum both in terms of severity as well as chronicity. There is a high prevalence of

gastroparesis in chronic pancreatitis patients, although the mechanism is poorly understood.[26] In addition, opioid use is strongly associated with delayed gastric emptying.[27,28]

Most patients undergoing TPIAT will have been evaluated preoperatively for the presence of gastroparesis. Many of these preoperative studies are suspect in the opinion of the authors, as a high percentage of patients will be on frequent narcotics around the period of gastric scintigraphy. In many cases, it is not feasible to discontinue opioids before testing. In patients with prominent gastroparesis symptoms, it is important to counsel patients that the TPIAT may make gastroparesis worse. Resection of the pylorus at the time of the TPIAT may be considered, or many patients can be referred for endoscopic therapy such as G-POEM for treatment of the gastroparesis.[29]

Data regarding the association between operative technique and delayed gastric emptying in TPIAT patients is limited. Many studies have evaluated the effects of various reconstructive techniques on postoperative delayed gastric emptying after pancreaticoduodenectomy for cancer, including pylorus resection and antecolic anastomosis of the duodenojejunostomy. However, randomized controlled trials are limited, and some studies have conflicting results.[30–32] There is a general finding that resection of the pylorus may lead to improved postoperative gastric emptying, with a potential effect on postoperative nutrition.[33]

In the immediate postoperative period after TPIAT, delayed gastric emptying is an expected finding. This is addressed with decompression via the gastric port of the gastrojejunal tube which is routinely placed intraoperatively. If there is concern for delayed gastric emptying once the patient has resumed oral intake, workup for gastroparesis includes a gastric emptying study as well as endoscopy.

We often find that delayed gastric emptying significantly improves by 4–6 weeks postoperatively. For those in which it does not improve, evaluation typically includes upper endoscopy to rule out the presence of a bezoar, as well as gastric emptying scintigraphy to assess for delayed gastric transit. Patients diagnosed with postoperative gastroparesis should receive counseling on appropriate dietary modifications and may benefit from targeted pharmacologic therapy. At our institution, such patients are routinely referred to a gastroenterology service with expertise in the management of gastrointestinal motility disorders. Lifelong dietary and lifestyle modifications are often necessary. A recent meta-analysis found only 2 pharmacological agents to be superior to placebo in the treatment of gastroparesis, clebopride, and domperidone.[29] Neither drug is FDA approved in the United States.

Gastrointestinal Dysmotility

Gastrointestinal dysmotility refers to the irregular movement of intestinal contents through the intestinal tract. For our purposes, this refers to dysmotility in the small intestine and/or colon. Some patients may have pre-existing dysmotility as a result of damage from pancreatitis, which is unlikely to resolve after TPIAT. In the immediate postoperative period, dysmotility is expected, with ileus being the extreme manifestation. Dysmotility that persists beyond 1–2 months is considered abnormal.

There are several possible mechanisms for long-term GI dysmotility following TPIAT.

This surgery causes significant changes to the innervation and hormonal regulation of the GI tract, which is known to affect GI motility.[19] Adhesive disease, which is common both with pancreatitis and after TPIAT, has been implicated as a mechanical cause of dysmotility.[34] In addition, there is emerging research regarding the role of the gut microbiome in mediating GI motility, as well as changes in the microbiome after undergoing surgery of the GI tract.[35,36] The role of the gut microbiome in long-term GI dysmotility following TPIAT is yet to be elucidated.

We caution against diagnosing GI dysmotility before a thorough workup of other contributing causes. That being said, with the extensive anatomical and hormonal changes that TPIAT represents, all patients are expected to have changes in the function of their GI tract. Most have a period of readjustment over several months in which they establish a new normal, but some patients go on to experience more life-limiting symptoms. Dietary modifications are often helpful. Prokinetic agents such as metoclopramide, linaclotide, or lubiprostone may be trialed and continued if helpful. In extreme cases involving colonic dysmotility, surgical options such as colectomy may be considered.

Occasionally, patients have experienced significant difficulty with intestinal failure of uncertain etiology. This can manifest with persistent nausea and vomiting despite the interventions above, or signs of intestinal malabsorption such as diarrhea with persistent weight loss and malnutrition. These patients may benefit from either tube feeds or, in severe cases, total parenteral nutrition.

Alkaline Reflux Gastritis

TPIAT patients are at risk of alkaline reflux gastritis due to alterations in pylorus function (resection or altered innervation), resulting in backflow of bilious contents which is damaging to gastric mucosa.[37] This typically presents as chronic epigastric pain, nausea, or bilious vomiting exacerbated by eating, months to years postsurgery. Alkaline reflux gastritis is more common in the setting of surgical reconstruction without a Roux limb (single limb loop reconstruction). This diagnosis can be confirmed by endoscopy and treatment consists of medical management, such as PPI therapy and sucralfate, as well as dietary modifications. In extreme cases, reoperation to create a Roux limb may become necessary.

Marginal Ulceration

Marginal ulcers are a risk for all patients following TPIAT, although the pathogenesis is not well understood. Marginal ulcers typically present with epigastric pain, nausea, or emesis but may also present as a gastrointestinal bleed. At our center, 35% of TPIAT patients presenting with gastrointestinal bleeding were found to have a marginal ulcer or anastomotic bleed, with a median time to development of 17 months.[38] Due to these findings, our institution has protocolized starting a proton pump inhibitor (PPI) for at least 1 year postoperatively or often indefinitely if no contraindications exist. If PPIs are stopped, gradual weaning may be considered to reduce rebound hyperacidity. Patients presenting with classic symptoms of gastritis or marginal ulcer, such as epigastric pain, pain relational to food intake, nausea, early satiety, or a burning characteristic should be evaluated by upper endoscopy. Of note, smokers are likely at increased risk of marginal ulceration following Roux-en-Y reconstruction.[39] Our center recommends smoking cessation before undergoing TPIAT.

Nephrolithiasis

Nephrolithiasis is a newly recognized long-term cause of abdominal or flank pain following TPIAT, with data from our institution demonstrating a 30% incidence of calcium oxalate kidney stones by 15 years following TPIAT.[40] The etiology of this is oxalate hyperabsorption, which is known to occur in conditions predisposing to fat malabsorption, including exocrine insufficiency. Under conditions of fat malabsorption, calcium binds to malabsorbed fat rather than to oxalate, leading to hyperabsorption of oxalate and risk for calcium oxalate stones. We recommend avoiding excessive intake of moderate to high oxalate foods after TPIAT. Adequate calcium intake or low dose calcium citrate supplementation with meals can further reduce risk of recurrence by acting as an oxalate binder in the gut.[41] Kidney stone episodes should be treated with usual approaches to nephrolithiasis, with either hydration and observation or intervention to remove the stone.

Bowel Obstruction

As with any intra-abdominal operation, the most common causes of postoperative bowel obstruction in TPIAT patients are adhesive disease and incisional hernias. This remains a lifelong risk following TPIAT. When bowel obstruction appears to be due to adhesive disease, we typically attempt conservative management with nasogastric decompression. Those with Roux-en-Y reconstruction are also at risk of bowel obstruction caused by internal hernia or afferent or efferent limb compression. Providers need a high index of suspicion not to miss this serious complication. A CT scan with oral contrast can aid in identifying such cases. These cases should undergo prompt evaluation for surgical management.

Some patients with adhesions experience recurrent obstructions. For these patients, we follow a typical protocol of conservative (nonoperative) management of small bowel obstruction unless contraindications exist. We often perform a Gastrografin challenge, which is useful both diagnostically and therapeutically.[42] In a subset of patients with recurrent, imaging-confirmed obstruction, elective adhesiolysis may be considered. Literature on abdominal adhesive disease more generally suggests that operative management in such cases can reduce the risk of recurrence and subsequent hospitalizations.[43] An important consideration in TPIAT patients is the complexity of their postoperative anatomy and gastrointestinal reconstruction. When elective adhesiolysis is indicated, we believe it is preferable for the original surgical team to perform the procedure whenever feasible, given their familiarity with the patient's anatomy.

Adhesive Disease

Some cases of chronic or recurrent abdominal pain are related to adhesive disease itself. Given the extensive resection and reconstruction in TPIAT, as well as significant peripancreatic inflammation and fibrosis, patients undergoing this operation tend to have more extensive adhesive disease. This can present as intermittent symptoms of partial obstruction, including nausea and pain related to oral intake, or can present more generally with persistent abdominal pain. Cine MRI captures intestinal motion and is an emerging technique for the diagnosis of adhesive disease.[44–46]

There is evidence to support the use of physical therapy, specifically soft tissue mobilization techniques, to treat abdominal pain related to adhesive disease.[47] We treat with both physical therapy and gabapentin if this etiology is suspected. In select patients, surgical adhesiolysis may be offered for either the indication of pain or of recurrent obstruction, as described above, related to adhesive disease. Unsurprisingly, we often find that patients have temporary relief from adhesiolysis and then develop recurrent symptoms. Thus, nonoperative interventions should be exhausted before attempting surgical management. We usually attempt nonoperative management for at least 1 year in these difficult cases.

Afferent Loop Syndrome

Afferent loop syndrome is a rare long-term complication after TPIAT, and refers to the buildup of luminal contents in the afferent limb of the reconstructed GI tract due to some form of distal obstruction.[48] The obstruction can be at the site of a distal anastomosis, from adhesions, strictures, internal hernia, or intussusception. In Roux-en-Y reconstruction, this usually refers to obstruction of the biliary limb. It can also occur in single-limb loop reconstruction.

Acute presentation is typically abdominal pain, nausea, and bilious vomiting and represents a surgical emergency as the buildup of pressure within the afferent limb can cause ischemia and perforation. This condition can also present in a more chronic fashion, in which the afferent limb is partially obstructed. When there is chronic stasis in the afferent limb, the patient is also at risk of developing ascending cholangitis, as well as small intestinal bacterial overgrowth (SIBO). Afferent loop syndrome can be diagnosed by a CT scan with oral contrast, in which dilation of the afferent limb becomes apparent. Technetium-99m HIDA hepatobiliary scanning can also be utilized; in afferent loop syndrome, it will show altered afferent limb emptying.[49] Surgery remains the mainstay of treatment and will depend on the underlying cause of obstruction. Occasionally, anastomotic ulceration causing stricture and subsequent afferent limb syndrome may be managed endoscopically with balloon dilations.[50]

Small Intestinal Bacterial Overgrowth

The etiology of small intestinal bacterial overgrowth (SIBO) following TPIAT is multidimensional, with alterations in small bowel motility, decreased gastric acid secretion (for patients on PPI therapy), and anatomic changes associated with TPIAT all playing potential roles in disrupting the normal homeostatic mechanisms surrounding the intestinal microbiome.[51] Patients with Roux-en-Y reconstruction may be at additional risk due to stasis in the afferent limb. SIBO has a variable presentation; patients may have symptoms of abdominal pain, bloating, nausea, vomiting, constipation, or changes in defecation habits such as diarrhea or constipation, flatulence, or soft stools.[52]

We often treat empirically for SIBO based on clinical symptoms, although a hydrogen breath test can also be considered. Typically patients respond quickly to antibiotic therapy, with improvement in their symptoms acting as a confirmation of the diagnosis. However, it is quite common to observe recurrent SIBO. This can pose significant challenges, especially if recurrent episodes become refractory to antibiotics. Optimization of pancreatic enzymes, nutritional and vitamin supplementation, and long-term dietary modifications are often necessary.

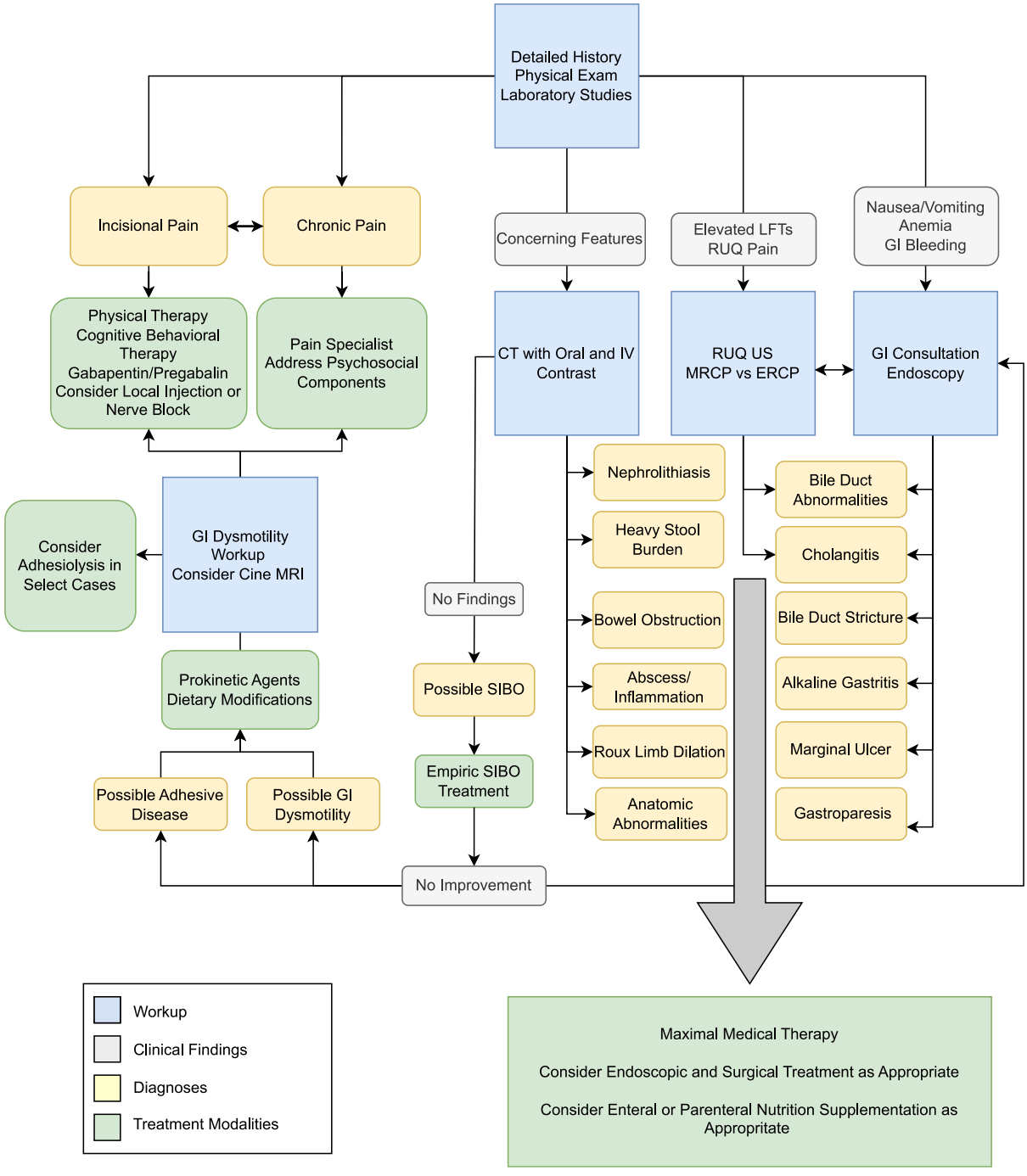

FIGURE 2. Workup and decision tree for patients presenting with abdominal pain after TPIAT (typically >6 mo postop).

Chronic Pain Syndrome/Central Sensitization

Chronic pain syndrome is a recognized cause of abdominal pain following TPIAT. This appears to be related to the degree and duration of pain experienced from chronic pancreatitis preoperatively.[9,53] Studies of chronic pancreatitis have shown alterations in pancreatic nerves, evidenced by an increase in nerve fiber diameter and other findings associated with neurogenic inflammation.[54] Increased neural hypertrophy and neural density in chronic pancreatitis correlates with the degree of abdominal pain experienced by the patient.[4,5] There are also changes in biomarkers specific to neuropathic pain.[6] Recent studies show pathophysiological changes in both peripheral and central processing of pain with chronic pancreatitis, similar to many neuropathic pain disorders.[7,8]

We do not have a modality to test clinically for this diagnosis, although there is emerging work in quantitative sensory testing, which is elucidating pain patterns in other chronic pain conditions.[55] This may prove beneficial in characterizing abdominal pain caused by central

sensitization in chronic pancreatitis and following TPIAT as well. Chronic pain syndrome should be a diagnosis of exclusion. There are many treatable etiologies of pain that require evaluation before a diagnosis of chronic pain syndrome or central sensitization, especially in the setting of a new recurrence of abdominal pain following TPIAT.

DISCUSSION

As described above, the differential and workup of abdominal pain following TPIAT is long and complex. An important and sometimes difficult responsibility of the provider is to distinguish between pain associated with normal postoperative recovery and the "new normal" of living with altered gastrointestinal anatomy versus pain indicating a problem that needs to be addressed. This can be especially difficult in TPIAT patients given their chronic pain state and opioid dependence going into surgery, and the slow weaning process postsurgery. A high index of suspicion is needed to diagnose many of the problems associated with TPIAT. Some of this comes down to clinical experience and gestalt.

Figure 2 describes our typical workup and subsequent management of common causes of abdominal pain after TPIAT that are not immediate postoperative issues (typically >6 mo following surgery). We emphasize the importance of taking a detailed history, including characterization of the pain, changes in the type of pain, and factors associated with it. There is an overlap between several etiologies of abdominal pain, which are common postoperatively in TPIAT patients. For example, opioid use and postoperative dysmotility related to altered anatomy may both contribute to obstipation. We may encounter a pitfall if we address obstipation while failing to recognize and modify contributing factors. Similarly, SIBO may be an entity in and of itself, or it may be a sign of anatomic problems such as afferent limb syndrome, adhesive disease, or dysmotility, which are causing stasis. An understanding of the underlying pathophysiology of each of these conditions is paramount in caring for patients living post-TPIAT.

CONCLUSION

As more patients undergo TPIAT, we must plan for and address the associated causes of abdominal pain, both in the short and long term. These causes are complex and often multifactorial, requiring a strong understanding of the patient's altered anatomy and physiology. We must also address the role that central sensitization and neuropathic pain play in chronic abdominal pain before and after TPIAT, and integrate this into operative decision-making and clinical management.

Patients with abdominal pain after TPIAT, like patients with chronic pancreatitis, will benefit from a multidisciplinary evaluation and long-term relationships with a multidisciplinary care team. We follow a sequential approach to the treatment of abdominal pain, which starts with conservative measures, such as lifestyle modifications and pharmacological management, before progressing to more invasive interventions. We emphasize the importance of regular reassessment and adjustment of the treatment plan based on the patient's response. Additional surgical management should be reserved for those who have failed this sequential approach or those with obvious surgical disease (eg, ascending cholangitis with stricture, anatomic small bowel obstruction).

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