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Chronic Abdominal Pain Disorders: Chronic Pancreatitis and Cyclic Vomiting Syndrome

Introduction

Disorders such as chronic pancreatitis and cyclic vomiting syndrome are characterized by chronic abdominal pain, nausea, and vomiting. The pain associated with these disorders often is refractory to analgesics, leaving emergency providers with the difficult task of relieving pain while simultaneously attempting to limit the use of opiates. In addition, some cases of chronic abdominal pain are secondary to substance abuse (e.g., alcohol in chronic pancreatitis, cannabis in cyclic vomiting syndrome), leading to frustration among some providers, who may perceive the disorders as self-inflicted. Moreover, the association of chronic abdominal pain disorders with comorbid psychiatric disorders, including anxiety and depression, can make the physician-patient interaction complex. Such challenges can lead to low patient satisfaction and medication noncompliance among patients and contribute to burnout among emergency providers.[1,2]

However, many of the perceptions of these pain disorders are misguided. For example, cyclic vomiting syndrome was recognized first in children, and the majority of cases are unrelated to substance use.[3] Many non-opiate treatments have been shown to be effective at managing symptoms in patients. Therefore, it is important for emergency providers to understand the pathophysiology and management of chronic abdominal pain disorders. This article will review two common chronic abdominal pain disorders encountered in the ED: chronic pancreatitis and cyclic vomiting syndrome.

Chronic Pancreatitis

Epidemiology

Both acute and chronic pancreatitis are characterized by inflammation and injury to the pancreas, although the progression and outcomes of the two diseases are significantly different. Less than 20% of patients who experience an episode of acute pancreatitis will develop recurrent episodes, and less than 10% will develop chronic pancreatitis.[4] "Recurrent acute pancreatitis" refers to separate episodes of pancreatitis due to an identifiable cause (e.g., gallstones) with a period of resolution between episodes.[5] "Chronic pancreatitis," in most consensus definitions, requires irreversible histologic or morphologic changes in the pancreas, usually with accompanying pain and long-term exocrine and endocrine dysfunction.[5] Most patients with chronic pancreatitis will have at least

EXECUTIVE SUMMARY

- Causes of chronic pancreatitis include alcohol and/or tobacco use, pancreatic duct obstruction, heredity, or autoimmune disease.
- Complications of chronic pancreatitis include diabetes, steatorrhea, splanchnic vein thrombosis with gastric varices, pseudocysts, pancreatic duct stricture, and pancreatic cancer.
- Cyclic vomiting syndrome was described first in children. Many cases are associated with migraine, anxiety, and/or depression. More recently, there has been an increase seen with frequent use of cannabis.
- Acute symptoms often respond to treatment with sumatriptan. Patients with cyclic vomiting due to cannabis should abstain from its use. Others find relief with hot showers, use of capsaicin cream, haloperidol, or benzodiazepines.

one preceding episode of acute pancreatitis, although one-third of patients lack a history of acute pancreatitis.[6] The histologic and morphologic changes needed to diagnose chronic pancreatitis can take months or years to develop, so it often is difficult to diagnose at an early stage.

In the United States, the incidence of chronic pancreatitis is four cases per 100,000 person-years. A higher incidence has been reported worldwide.[7] Chronic pancreatitis is more common in men and African Americans and usually is diagnosed in the fifth or sixth decade of life, but it can develop at younger ages.[5] Patients with chronic pancreatitis have high rates of healthcare utilization and medical costs, mainly because of the chronic pain associated with the disease and its complications.[8] In the United States, chronic pancreatitis results in an aggregate cost of more than $150 million annually.[9]

Etiology

The pancreas has endocrine and exocrine functions. Its endocrine function involves secreting insulin and glucagon, and its exocrine function is to secrete digestive enzymes.[10] In patients with chronic pancreatitis, there is repeated stress or injury to the pancreas, which leads to destruction of acinar cells and subsequent release of pancreatic enzymes into the interstitium of the pancreas. Eventually, this leads to necrosis and fibrosis of the organ.[11,12] An episode of acute pancreatitis may or may not serve as the sentinel event in the development of chronic pancreatitis.[13] Some common inciting factors are described in the following section.

Alcohol. Alcohol is the most common cause of chronic pancreatitis and accounts for 50% of cases.[5] The non-esterified esters in alcohol induce acinar cell injury and inflammation.[14] Cumulative exposure to alcohol, including the amount and duration of alcohol use, is the most important determinant for the development of chronic pancreatitis. Consuming four to five alcoholic drinks daily doubles the risk of developing chronic pancreatitis.[15,16] Because of gender differences in alcohol absorption and metabolism, women have a higher risk of developing chronic pancreatitis at lower levels of alcohol intake.[17,18] On average, it takes 18 years between the start of excess alcohol intake and the diagnosis of chronic pancreatitis.[19] In patients with acute pancreatitis secondary to alcohol, 25-50% will develop recurrent pancreatitis and, among those patients, 42-80% will develop chronic pancreatitis.[20,21] However, many patients who develop chronic pancreatitis secondary to alcohol lack a history of acute pancreatitis.[22] Progression of established chronic pancreatitis can be halted or slowed if a patient stops drinking alcohol.[5]

Tobacco. Smoking tobacco increases the risk of developing chronic pancreatitis in a dose-dependent manner independently from alcohol, although there is a cumulative risk in patients who smoke and drink alcohol.[23] Nicotine induces oxidative stress in the pancreas via several pathways, which damages acinar cells and leads to fibrosis.[24] Smoking cessation has been shown to decrease disease progression in patients with established chronic pancreatitis.[25]

Pancreatic Duct Obstruction. Pancreatic duct obstruction, secondary to strictures, stones, or extrinsic compression, causes increased pressure in the pancreatic duct and can lead to fibrosis and chronic pancreatitis.[26] Pancreatic duct strictures may form after an acute episode of gallstone-induced pancreatitis, endoscopic/surgical procedure, or blunt injury.[5] Pancreatic ducts also can be blocked by stones (often the consequence of already established chronic pancreatitis) or extrinsic compression from a pancreatic or intestinal tumor.[27,28] It is controversial whether pancreas divisum, a common and congenital anatomic variation of the pancreas, can cause pancreatic duct obstruction and subsequent chronic pancreatitis.[5]

Hereditary Chronic Pancreatitis. A number of genetic mutations, including *PRSS1*, *CFTR*, and *SPINK*, induce stress in the acinar cells and have been connected with development of chronic pancreatitis.[14,29-34] Patients with hereditary pancreatitis usually experience episodes of acute pancreatitis in childhood and develop signs of chronic pancreatitis by the third decade of life.[35]

Chronic Autoimmune Pancreatitis. The most common type of autoimmune pancreatitis is associated with a rare inflammatory multiorgan syndrome known as immunoglobulin G4 (IgG4)-related inflammatory disease.[7] Rather than presenting with abdominal pain, many patients with autoimmune pancreatitis initially present with painless jaundice.[36] Often it can be difficult to distinguish chronic autoimmune pancreatitis from pancreatic cancer.[37] Serologic tumor markers (e.g., Ca 19-9), imaging, and pancreatic biopsy may help to differentiate autoimmune pancreatitis from pancreatic cancer. In addition, unlike pancreatic cancer and most forms of chronic pancreatitis, autoimmune pancreatitis responds

Table 1. Complications of Chronic Pancreatitis

- Chronic abdominal pain
- Type 3c diabetes
- Steatorrhea
- Pancreatic pseudocyst
- Common bile duct or pancreatic duct stricture
- Duodenal stenosis or obstruction
- Gastric varices secondary to portal vein thrombosis
- Pancreatic ascites
- Pancreatic cancer
- Pleural effusion
- Osteopenia and osteoporosis
- Splenic vein thrombosis

rapidly to steroids, and disease progression often can be halted.

Pathophysiology

In patients with chronic pancreatitis, oxidative stress either from exogenous (e.g., alcohol) or endogenous (e.g., genetic) sources induces injury to the pancreatic acinar cells. The cells release calcium and pancreatic enzymes, which cause destruction and fibrosis of the adjacent parenchyma. Subsequent inflammation also can cause pancreatic duct obstruction, leading to pancreatic ductal hypertension, resultant hypoperfusion, and further injury to pancreatic cells.[7] Typically, this inflammation and fibrosis cause abdominal pain, although some patients may develop chronic pancreatitis without experiencing symptoms. Destruction of pancreatic cells leads to early endocrine dysfunction and the development of diabetes. Exocrine dysfunction develops later in the disease and presents with steatorrhea and diarrhea.[38]

Clinical Features

The clinical features of chronic pancreatitis vary depending on its etiology. Chronic pancreatitis secondary to alcohol, for example, typically has an aggressive course, whereas chronic pancreatitis due to other etiologies has a more indolent course.

Abdominal Pain. Abdominal pain is the presenting symptom in 90% of patients with chronic pancreatitis.[39] (*See Table 1.*) A minority of patients will have no pain. The abdominal pain usually is epigastric, worse with meals, and partially relieved with leaning forward. The pain associated with chronic pancreatitis is multifactorial in nature and may be due to inflammation of the parenchymal nerve sheaths, increased pressure in the pancreatic ducts, tension in the pancreatic capsule, or complications of the disease, such as gastric ulcers.[40]

Diabetes. Endocrine insufficiency develops in 80% of patients with chronic pancreatitis, leading to pancreatogenous or "type 3c" diabetes.[41] Approximately 5% of all diabetes is attributed to type 3c diabetes, which is diagnosed by excluding other sources of diabetes and fulfilling criteria for both chronic pancreatitis and diabetes.[42] Types 1 and 2 diabetes are not independent risk factors for chronic pancreatitis. Patients with type 3c diabetes are at high risk of developing episodes of both hyperglycemia and hypoglycemia, due to concomitant loss of glucagon and other glucose-regulating hormones that are produced by the pancreas.[7]

Steatorrhea. Steatorrhea, defined as greater than 7 grams of fat content in the stool per day, occurs if lipase levels drop to less than 10% of normal.[43] It is usually a late manifestation of chronic pancreatitis and can result in deficiencies of fat-soluble vitamins (vitamins A, D, E, and K) and malnutrition.

Splanchnic Vein Thrombosis. Splanchnic vein thrombosis (most commonly the splenic vein) can occur in both acute and chronic pancreatitis. Most patients are asymptomatic, although some develop gastric varices and subsequent gastrointestinal bleeding. Splanchnic vein thrombosis can be diagnosed with abdominal ultrasound or computed tomography with intravenous contrast. Anticoagulation is not started, although elective embolization of the spleen may be performed to prevent the development of gastric varices.[44]

Pancreatic Pseudocysts. Approximately 20-40% of patients with chronic pancreatitis develop pancreatic pseudocysts, which are collections of pancreatic fluid encased in inflammatory walls.[45] (*See Figure 1.*) The majority of pseudocysts remain asymptomatic and can be observed.[46] Intervention is warranted in patients with pseudocysts who develop chronic abdominal pain, early satiety with weight loss, gastric outlet obstruction, biliary obstruction, infection, fistula formation, or pancreatic duct stones.[47] Typically, patients develop symptoms or complications from pseudocysts that are > 5 cm in diameter.[40]

Pancreatic Duct Strictures. Many patients with chronic pancreatitis develop pancreatic duct strictures, which can lead to increased pressure in the pancreatic duct and subsequent pain.[51,52] Most pancreatic duct strictures are benign; however, malignancy should be excluded. Approximately 10% of patients with pancreatic duct strictures develop biliary cirrhosis or cholangitis.[52] Endoscopic treatment of benign pancreatic duct strictures is indicated if patients develop secondary biliary cirrhosis, common bile duct stones, persistent jaundice, or significant pain.[53]

Pancreatic Cancer. About 5% of patients who have chronic pancreatitis will develop pancreatic cancer.[54-58] (*See Figure 2.*) The cumulative incidence of pancreatic cancer is 2% per decade after diagnosis of chronic pancreatitis.[56] Higher rates of alcohol use and tobacco smoking in these patients likely contribute to the increased overall risk of cancer.[57,59] Without surgical resection, the life expectancy of patients with chronic pancreatitis and pancreatic cancer is less than one year. If a tumor is found and resected in a timely manner, five-year survival improves to 20-25%.[40]

Morbidity and Mortality. Patients with chronic pancreatitis typically report a decreased quality of life, which is thought to contribute to high rates of unemployment and low income in these patients.[60] Patients with chronic pancreatitis have 2.5-times higher mortality than sex- and age-matched controls.[61-63] Part of the increased mortality is due to the comorbidities associated with chronic pancreatitis, such as diabetes and peptic ulcer disease. The most common causes of death in patients with chronic pancreatitis are malignancy (22-23%) and cardiovascular disease (12-21%).[61,63]

Diagnostic Studies

Given that acinar cell destruction leads to decreased enzyme production

in patients with chronic pancreatitis, serum levels of pancreatic enzymes, such as lipase, are unreliable markers of disease. As a result, imaging generally is required to diagnose chronic pancreatitis and its complications.

Endoscopic ultrasound, with or without contrast, is considered the best imaging modality for chronic pancreatitis, although it generally is not available in the ED.[10,64,65] Transabdominal ultrasound can be used to detect large pseudocysts. Computed tomography and magnetic resonance imaging are insensitive for identification of early stages of chronic pancreatitis, although they may detect complications of late disease, including pancreatic calcifications, ductal changes, pancreatic atrophy, pseudocysts, and malignancy.[10,66] Endoscopic retrograde cholangiopancreatography (ERCP) rarely is used for diagnostic purposes and largely has been replaced by endoscopic ultrasound.[10]

Figure 1. Computed Tomography Demonstrating a Pseudocyst (Star) in a Patient With Chronic Pancreatitis

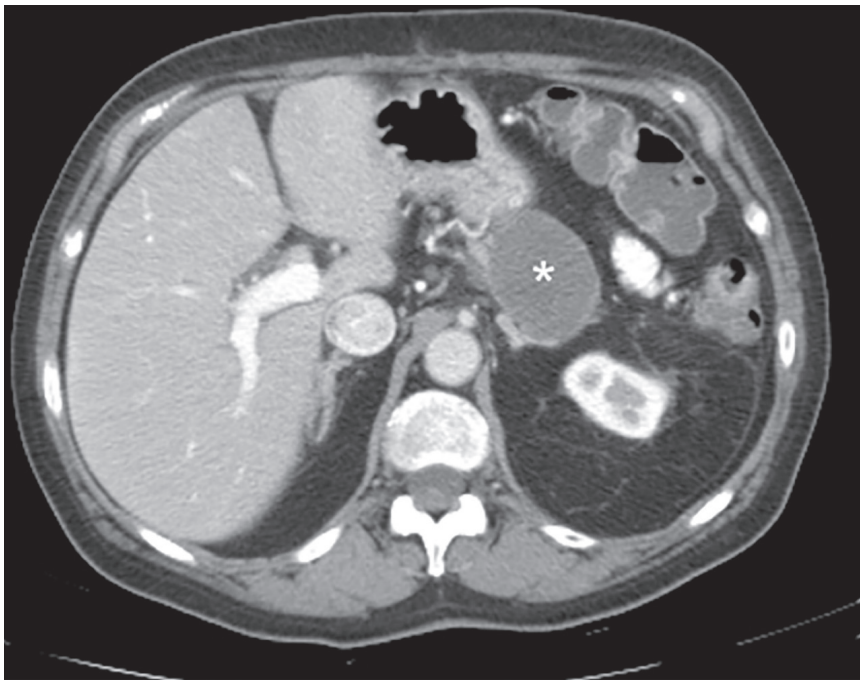


Image used with permission from: David Guez, MD

Management

In most cases of chronic pancreatitis, there is no specific treatment to halt disease progression aside from alcohol and smoking cessation. Management is mainly symptom control. Medical management, consisting of analgesics and pancreatic enzyme supplementation, is effective at treating symptoms in approximately 50% of patients.[14] It is less effective in patients who continue to drink alcohol or smoke.[67] Patients with diabetes will require insulin, and pancreatic enzyme-replacement therapy usually is started in patients with exocrine insufficiency.[7]

Endoscopic Treatments. Endoscopic techniques to decompress pancreatic duct stones and strictures and drain pseudocysts have been shown to relieve pain in 65% of patients.[51] Endoscopic treatment of pancreatic duct strictures typically consists of pancreatic sphincterectomy, followed by stent placement.[68,69] The duration of stent therapy is controversial, and stent occlusion is common.[70] Endoscopic techniques to remove pancreatic duct stones via retrograde access of the pancreatic duct include pancreatic sphincterotomy, forceps, or employment of extraction balloons or baskets.[26,71,72] Simultaneous endoscopic extracorporeal shock wave lithotripsy is also performed to clear stones.[73,74] Complications of these procedures include bleeding, iatrogenic pancreatitis, duct perforation, stent migration, infection, and sphincter stenosis.[26]

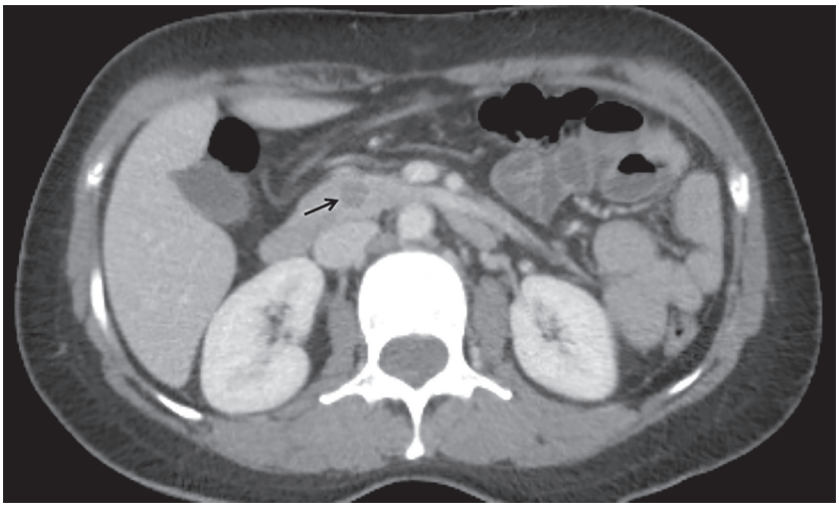
Surgical Treatments. Surgical options in patients with severe pain related to chronic pancreatitis include partial pancreatic resection and total pancreatectomy, with or without islet cell auto-transplantation. Studies regarding the optimal timing for surgery to treat painful chronic pancreatitis are limited, although there is some evidence that surgery is more effective if performed early in the disease course.[76,77] Cases of infected pancreatic necrosis may be managed conservatively with antibiotics or surgical debridement.[40]

Novel Therapies. Some novel therapies to decrease inflammation and subsequent fibrosis are in the experimental phase.[14] Cannabinoid-2-receptor agonists have been shown to decrease pain associated with chronic pancreatitis and protect tissue from fibrosis.[78] Some immunomodulatory agents are effective in animal models but are not yet available for humans.[79,80] Spinal cord stimulation has shown promise in decreasing pain and daily opioid requirement in patients with chronic pancreatitis.[81]

Additional Aspects

Management of Chronic Pain. Chronic stimulation of pancreatic pain receptors in patients with chronic pancreatitis is thought to lead to abnormal pain processing and neural remodeling in the central nervous system, known as "central sensitization."[82-85] As a result, patients develop a maladaptive response to pain that can be difficult to manage. Acetaminophen is recommended as the first-line analgesic for chronic pain.[86] Other non-opiate medications shown to be effective in the treatment of pain associated with chronic pancreatitis include gabapentin, pregabalin, selective serotonin reuptake inhibitors, and tricyclic antidepressants (TCA).[7,87] Sub-anesthetic doses of ketamine have been used in children and adults, although evidence for its efficacy is limited.[88-90] There is conflicting evidence about whether antioxidants are effective at relieving pain.[91,92]

Figure 2. Computed Tomography Demonstrating Pancreatic Cancer (Arrow)



Nonsteroidal anti-inflammatory drugs should be avoided because of the risk of stomach ulcers in patients. Alcohol and smoking cessation also have been shown to decrease pain and should be encouraged.[25]

Patients with chronic pancreatitis often require oral opiates for severe pain; however, only 25% of patients are likely to benefit from opioid treatment.[93] Tramadol has been shown to be as effective as morphine, although with a better side-effect profile, making it the preferred first-line opioid.[94]

Pediatric Chronic Pancreatitis. Acute pancreatitis that occurs in children usually is secondary to biliary obstruction, systemic illnesses, or medications. Up to 30% of cases are idiopathic.[101] Of children with acute pancreatitis, 15-35% will develop recurrent or chronic pancreatitis; the most common predisposing factor is genetic mutation.[102] Similar to adults, children with chronic pancreatitis experience significant pain and may develop type 3c diabetes and exocrine insufficiency. Transabdominal ultrasound is the preferred imaging modality in children because of the lack of ionizing radiation.[101] There is increased emphasis on opioid-free management of the condition in children.

Disposition

In patients with chronic pancreatitis who present to the ED with abdominal pain, it is important to ascertain the etiology of the pain. If the pain is secondary to an exacerbation of chronic pain and can be managed successfully with oral analgesics, patients may be discharged home. Patients with clinical or radiologic signs of infection, such as infected pancreatic necrosis or an infected pseudocyst, require admission for antibiotics and potential debridement or drainage. Antibiotics usually are not given to patients with sterile necrosis or prophylatically.[103] Unless there is an associated paralytic ileus, enteral nutrition should be encouraged in admitted patients, as parenteral nutrition can lead to intestinal villous atrophy, bacterial translocation, and subsequent infection of necrotic tissue.[104,105] Stress ulcer prophylaxis is recommended in admitted patients, given the risk of gastrointestinal ulcers.[40]

Patients who are discharged should be counseled on alcohol and smoking cessation. Patients typically are referred to primary care for preventive care (e.g., cancer screening), gastroenterology, and a pain management specialist.

Cyclic Vomiting Syndrome

Epidemiology

Cyclic vomiting syndrome is characterized by recurrent, self-limited, and often incapacitating episodes of nausea and vomiting that are separated by periods free of symptoms.[106,107] It was described first in children in 1882.[3] The prevalence of cyclic vomiting syndrome is estimated to be 2% in school-age children and is unknown in adults, although it may account for up to 14% of cases of unexplained nausea and vomiting in adults.[107-109] Patients most commonly are white (63%) and female (63%).[106,110] The mean age of onset in children is approximately 5 years of age, although diagnosis typically is not made until age 9 years.[111] In adults, the mean age of onset and diagnosis is 20 to 30 years.[106,107]

The average cost of an inpatient admission for cyclic vomiting syndrome is nearly $20,000, which does not include costs related to missed work or outpatient studies.[110] High rates of medical recidivism have been associated with difficulties managing the disorder and frustration among patients and physicians regarding its often-unclear etiology.[110] Despite a recent increase in published literature about the disorder in both children and adults, the diagnosis often is missed or misdiagnosed in the ED.[107,112]

Etiology

The etiology of cyclic vomiting syndrome likely is multifactorial and variable across patients, as many conditions and comorbidities have been linked to the disorder. Triggers of cyclic vomiting syndrome are identified more commonly in children and can be found in 80% of patients.[108]

Comorbidities

Headache. Patients with cyclic vomiting syndrome often have a personal or family history of headaches.[108,110,111,113] Many children and adults also eventually develop migraines, and studies have demonstrated similar electroencephalogram changes in patients with cyclic vomiting syndrome and migraines.[114] It is thought that cyclic vomiting syndrome and migraines may exist on a spectrum of pathology; cyclic vomiting syndrome is considered a subgroup of migraines.[107,115] (*See Table 2.*)

Substance Use. Recently, there have been increased reports of cyclic vomiting syndrome related to cannabis use, although opiates and nicotine have been implicated in the disorder

Table 2. Differential Diagnosis of Patients Presenting With Cyclic Vomiting Syndrome

Gastrointestinal disorders	• Mechanical: bowel obstruction, malrotation, hernia, volvulus, intussusception, malignancy • Functional: gastroparesis • Inflammatory diseases: appendicitis, pancreatitis, gastritis, peptic ulcer disease, and inflammatory bowel disease • Hepatobiliary disease: cholecystitis, acute liver failure, hepatitis • Infections: viral (e.g., adenoviruses) and bacterial
Neurologic disorders	• Space-occupying lesions: intracranial hemorrhage, tumor • Primary headache disorders (e.g., migraine) • Epilepsy
Metabolic disorders	• Acquired: diabetic ketoacidosis, uremia secondary to renal disease, adrenal disease, thyroid disease • Hereditary: fatty acid oxidation and mitochondrial disorders
Medications and toxins	• Antibiotics, chemotherapy • Alcohol and illicit drug use or withdrawal
Urologic and gynecologic disorders	• Kidney stones • Ovarian torsion • Hyperemesis gravidarum

as well.[110] Cannabis has been used for brief periods to treat nausea in some patients. However, its long-term use has been shown to induce cyclic vomiting syndrome. It is thought that chronic use leads to fat tissue accumulation of δ-9-tetrahydrocannabinol (THC), a lipophilic compound in cannabis. During times of stress, lipolysis releases a large amount of THC into the circulation and induces nausea.[115] Abstinence from cannabis resolves symptoms in some, but not all, patients.[115]

Psychiatric Disease. Patients with cyclic vomiting syndrome often have concurrent anxiety or depression, although a causal relationship has not been identified.[108,110,114,116] An estimated 44% of cases of cyclic vomiting syndrome can be attributed to psychological stress.[108] Treating comorbid anxiety has been shown to improve clinical outcomes in patients with cyclic vomiting syndrome.[117] It is recommended that patients who present with symptoms of cyclic vomiting syndrome be screened for psychiatric illness.

Other Associations. Cyclic vomiting syndrome is associated with gastroesophageal reflux disease, gastroparesis, infections (most commonly upper respiratory infections), diabetes mellitus, sleep deprivation, medications, menses, and pregnancy.[107,109-111,115,119] Excitement and emotional stress are common triggers in children.[114]

Pathophysiology

The exact pathophysiology of cyclic vomiting syndrome is unclear.[113,115] Given the similarities with migraines (e.g., episodic attacks, stereotyped onset), cyclic vomiting syndrome, like migraines, may be the result of autonomic dysfunction.[108,109] Another theory implicates the brain-gut neuroendocrine axis.[107,108,115,118] Normally, the hypothalamus releases corticotropin-releasing factor (CRF), which stimulates downstream release of adrenocorticotropic hormone (ACTH) and antidiuretic hormone (ADH). In patients with cyclic vomiting syndrome, elevated ACTH and ADH levels are seen, which is thought to be due to stress-induced release of CRF and leads to delayed gastric emptying and vomiting.[108,113] TCAs are known to inhibit the CRF gene and have been shown to be effective in the treatment of cyclic vomiting syndrome.[108] Another theory has linked mitochondrial DNA mutations with cyclic vomiting syndrome in children, although this has not been demonstrated in adults with the disorder.[115]

Clinical Features

Often it is difficult to diagnose cyclic vomiting syndrome in the ED. Up to one-third of patients with cyclic vomiting syndrome also develop low-grade fever and diarrhea, making it difficult to distinguish from gastroenteritis.[119] Up to 70% of patients with cyclic vomiting syndrome have abdominal pain, which broadens the differential diagnosis.[108] In addition, symptoms of cyclic vomiting syndrome are highly variable between patients, although they usually are consistent within one individual.[111] One study found that it takes a median of 15 ED visits and five to six years of symptoms to reach a diagnosis of cyclic vomiting syndrome.[109]

The Rome IV criteria were developed to assist in the diagnosis of cyclic vomiting syndrome. Patients must have each of the following for at least six months before meeting diagnostic criteria for the condition: stereotypical episodes of acute-onset vomiting that last less than one week; at least three discrete episodes in the previous year and two episodes in the past six months that occur at least one week apart; and absence of symptoms between episodes.[109]

Episodes of nausea and vomiting associated with cyclic vomiting syndrome are characterized by four distinct phases. In the pre-emetic period, a patient experiences pallor, diaphoresis, and nausea. In the intense emesis period, a patient can have up to 30 episodes of emesis daily, and also may develop abdominal pain or diarrhea. This is followed by the recovery phase, in which the nausea and vomiting gradually resolve, and the inter-episodic phase, in which the patient is symptom-free.[109] Episodes of cyclic vomiting syndrome generally are more prolonged and frequent in adults than in children. In addition, some adults progress to a "coalescent stage," characterized by subacute symptoms and near-continuous nausea.[108]

Diagnostic Studies

Emergency providers are unlikely to diagnose a patient with the condition in the ED. However, certain laboratory

Table 3. Abortive Treatments for Cyclic Vomiting Syndrome

Environmental	Place patient in a dark, quiet room
Abortive	Sumatriptan (patients > 12 years of age) • Subcutaneous: 6 mg/dose, maximum 12 mg daily • Intranasal: 20 mg/dose, maximum 40 mg daily • Oral: 50 mg/dose
Hydration	• Dextrose 5-10% solution with potassium replacement (if hypokalemic)
Anti-nausea medications	Ondansetron, prochlorperazine, chlorpromazine
Sedatives	Lorazepam, diphenhydramine
Pain medications	Nonsteroidal anti-inflammatory drugs, acetaminophen, opiates
Experimental	Haloperidol, topical capsaicin cream

Table 4. Preventive Treatments for Cyclic Vomiting Syndrome

Environmental	Avoidance of triggers (e.g., cannabis)
Medications	Tricyclic antidepressants, cyproheptadine, anticonvulsants, vitamins

and imaging studies rule out more emergent pathologies. For example, a patient with multiple ED visits for nausea and vomiting, with prior laboratory (e.g., lipase, hepatic function tests) and imaging studies that are unremarkable, ultimately may be diagnosed with cyclic vomiting syndrome.[108,120,121]

Management

Many treatments for cyclic vomiting syndrome are based on pediatric studies or anecdotal evidence and lack robust evidence.[122] In adults, sumatriptan has been shown to treat symptoms effectively in 56-83% of patients and is considered the first-line abortive treatment.[108,111,115,116,121-123] (*See Table 3.*) It is approved only for patients older than 12 years of age.[121] Side effects of sumatriptan include neck pain and vasospasm.[121] Dextrose-containing solutions with potassium replacement (if the patient is hypokalemic from vomiting) are recommended for intravenous hydration.[107,115,121] Diphenhydramine (an H1-histamine antagonist) and ondansetron (a 5-HT antagonist) are used routinely to treat nausea in adults.[116] In children, diphenhydramine and prochlorperazine are used commonly to treat nausea.[115] If antiemetics fail, an anxiolytic/sedative, such as lorazepam, can be used.[108,111,121] Nonsteroidal anti-inflammatory drugs, such as ketorolac, typically are used to treat pain. Opioids should be used cautiously because of the risks of misuse and dependence as well as rebound symptoms.[115]

TCAs have been shown to be the most effective medications for long-term preventive therapy in both children and adults, with greater than 75% of patients achieving symptom resolution.[116] (*See Table 4.*) In patients older than 5 years of age, amitriptyline is the first-line agent. In children younger than 5 years of age, cyproheptadine (a histamine-receptor antagonist) is preferred.[111] Side effects of TCAs include behavioral changes, somnolence, constipation, and arrhythmias.[121,123] Less commonly used medications that also are effective in preventing cyclic vomiting symptoms include propranolol, anticonvulsants (e.g., zonisamide, phenytoin), and vitamins (e.g., coenzyme Q10, L-carnitine, riboflavin). Long-term preventive medications usually are not initiated in the ED without first consulting a gastroenterologist.[109,111,121,124,126]

In patients with cyclic vomiting syndrome secondary to cannabis use, abstinence from cannabis alleviates symptoms in up to 97% of patients.[127] However, given the popular perception that cannabis relieves nausea, it often is difficult to convince patients to quit. There is anecdotal evidence that hot showers, benzodiazepines, haloperidol, and topical capsaicin cream also are effective treatments for symptoms associated with cyclic vomiting secondary to cannabis, although the exact mechanisms of action are unclear.[127-129] Administration of haloperidol 5 mg intravenously or orally is effective in acute exacerbations of cyclic vomiting syndrome; however, it has the risk of inducing ventricular tachyarrhythmias in patients with prolonged QT intervals.[128,130]

Disposition

Patients with uncontrolled symptoms, dehydration, or electrolyte disturbances may require admission.[119] Patients who are well enough to be discharged should be referred to a gastroenterologist for follow-up care. Generally, prophylactic medications are prescribed from the ED only after consultation with a gastroenterologist.

Conclusion

Patients with chronic abdominal pain disorders, including chronic pancreatitis and cyclic vomiting syndrome, commonly present to the ED with exacerbations of pain, nausea, and emesis. It is important for emergency providers to be aware of non-opiate treatments of pain, not only to avoid opiate side effects and misuse among patients, but also to prevent "central sensitization" and a maladaptive pain response from long-term opiate use. Rather than prescribing opiates, emergency providers should consider alternatives, such as pregabalin and gabapentin, in chronic pancreatitis, and sumatriptan in cyclic vomiting syndrome.

In addition to knowing how to control symptoms in patients with chronic

abdominal pain disorders, providers also should be aware of emergent complications associated with the disorders. As described in this article, patients with chronic pancreatitis may present with episodes of either hyperglycemia (secondary to type 3c diabetes) or hypoglycemia. Finally, given the increased risk of pancreatic cancer, emergency providers should know how to counsel their patients on alcohol and drug cessation and to provide appropriate outpatient referrals.

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CME/CE Questions

1. Which of the following statements is true regarding chronic pancreatitis?
   a. It most commonly affects white females.
   b. The most common etiology is gallstones.
   c. Some patients do not have a preceding episode of acute pancreatitis.
   d. Most cases respond to steroids.
2. Which of the following statements is true of chronic pancreatitis?
   a. Patients with chronic pancreatitis are at risk of developing hyperglycemic and hypoglycemic episodes.
   b. Steatorrhea is an early feature of chronic pancreatitis.
   c. Nearly all patients with chronic pancreatitis develop pancreatic pseudocysts.
   d. The majority of pancreatic duct strictures that form in patients with chronic pancreatitis are malignant.
3. Which of the following statements is true regarding treatment of chronic pancreatitis?
   a. Nearly all chronic pancreatitis patients report symptom resolution with an appropriate regimen of oral pain medications and pancreatic enzyme supplementation.
   b. Pancreatic duct stents that are placed for pancreatic duct stricture remain in place for life and rarely become occluded.
   c. Early surgical intervention may lead to better outcomes in patients with painful chronic pancreatitis.
   d. Opiates are the first-line analgesic for painful chronic pancreatitis.
4. Which of the following is true regarding cyclic vomiting syndrome?
   a. Patients most commonly are Caucasian and female.
   b. In most patients, no trigger is identified.
   c. The diagnosis is a relatively new phenomenon that originated after the widespread legalization of cannabis.
   d. Abdominal pain is required in the diagnosis of cyclic vomiting syndrome.
5. Which medication has been shown to be the most effective at treating acute symptoms associated with cyclic vomiting syndrome?
   a. Ondansetron
   b. Sumatriptan
   c. Cyproheptadine
   d. Amitriptyline
6. A 17-year-old male with a history of cyclic vomiting syndrome, substance abuse, and depression is brought in by ambulance for altered mental status after having a witnessed seizure at home. Per the family member, he has been taking an antidepressant that treats both his cyclic vomiting syndrome and depression. On examination, the patient has a pulse of 120 and is somnolent, with intermittent episodes of vomiting. Which diagnostic test is most likely to reveal the etiology of the patient's symptoms?
   a. Electrocardiogram
   b. Chemistry panel
   c. Alcohol level
   d. Head CT

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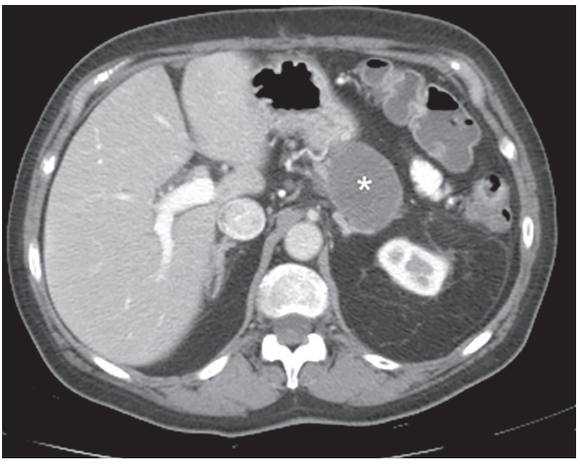

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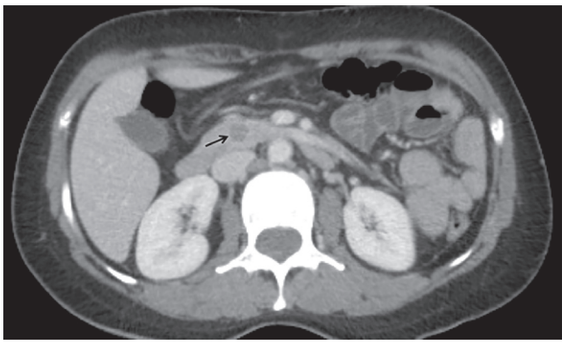
Complications of Chronic Pancreatitis

- Chronic abdominal pain
- Type 3c diabetes
- Steatorrhea
- Pancreatic pseudocyst
- Common bile duct or pancreatic duct stricture
- Duodenal stenosis or obstruction
- Gastric varices secondary to portal vein thrombosis
- Pancreatic ascites
- Pancreatic cancer
- Pleural effusion
- Osteopenia and osteoporosis
- Splenic vein thrombosis

Computed Tomography Demonstrating Pancreatic Cancer (Arrow)



Differential Diagnosis of Patients Presenting With Cyclic Vomiting Syndrome

Gastrointestinal disorders	• Mechanical: bowel obstruction, malrotation, hernia, volvulus, intussusception, malignancy • Functional: gastroparesis • Inflammatory diseases: appendicitis, pancreatitis, gastritis, peptic ulcer disease, and inflammatory bowel disease • Hepatobiliary disease: cholecystitis, acute liver failure, hepatitis • Infections: viral (e.g., adenoviruses) and bacterial
Neurologic disorders	• Space-occupying lesions: intracranial hemorrhage, tumor • Primary headache disorders (e.g., migraine) • Epilepsy
Metabolic disorders	• Acquired: diabetic ketoacidosis, uremia secondary to renal disease, adrenal disease, thyroid disease • Hereditary: fatty acid oxidation and mitochondrial disorders
Medications and toxins	• Antibiotics, chemotherapy • Alcohol and illicit drug use or withdrawal
Urologic and gynecologic disorders	• Kidney stones • Ovarian torsion • Hyperemesis gravidarum

Abortive Treatments for Cyclic Vomiting Syndrome	
Environmental	Place patient in a dark, quiet room
Abortive	Sumatriptan (patients > 12 years of age) • Subcutaneous: 6 mg/dose, maximum 12 mg daily • Intranasal: 20 mg/dose, maximum 40 mg daily • Oral: 50 mg/dose
Hydration	• Dextrose 5-10% solution with potassium replacement (if hypokalemic)
Anti-nausea medications	Ondansetron, prochlorperazine, chlorpromazine
Sedatives	Lorazepam, diphenhydramine
Pain medications	Nonsteroidal anti-inflammatory drugs, acetaminophen, opiates
Experimental	Haloperidol, topical capsaicin cream

Preventive Treatments for Cyclic Vomiting Syndrome	
Environmental	Avoidance of triggers (e.g., cannabis)
Medications	Tricyclic antidepressants, cyproheptadine, anticonvulsants, vitamins

Supplement to *Emergency Medicine Reports*, August 1, 2018: "Chronic Abdominal Pain Disorders: Chronic Pancreatitis and Cyclic Vomiting Syndrome." Authors: Caleb P. Canders, MD, Department of Emergency Medicine, UCLA Ronald Reagan Medical Center, Los Angeles; Brian V. Truong, MD, Department of Emergency Medicine, UCLA Ronald Reagan Medical Center, Los Angeles; Kellie M. Kitamura, MD, Department of Emergency Medicine, UCLA Ronald Reagan Medical Center, Los Angeles.