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NARRATIVE REVIEW

Charles J. Kahi, Section Editor

Rare, Overlooked, or Underappreciated Causes of Recurrent Abdominal Pain: A Primer for Gastroenterologists

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This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e1. Upon completion of this CME activity successful learners will be able to differentiate between appropriate diagnostic and treatment strategies for recurrent abdominal pain syndrome.

Recurrent abdominal pain is a common reason for repeated visits to outpatient clinics and emergency departments, reflecting a substantial unmet need for timely and accurate diagnosis. A lack of awareness of some of the rarer causes of recurrent abdominal pain may impede diagnosis and delay effective management. This article identifies some of the key rare but diagnosable causes that are frequently missed by gastroenterologists and provides expert recommendations to support recognition, diagnosis, and management with the ultimate aim of improving patient outcomes.

Keywords: Chronic Abdominal Wall Pain; Vascular; Porphyria; Allergic; Familial Mediterranean Fever.

Abdominal pain is the most common gastrointestinal (GI) symptom leading to ambulatory medical visits, with 19.4 million total visits (6.9 million office visits and 12.5 million emergency department [ED] visits) reported in the United States in 2016.[1] In 2018, the annual U.S. healthcare expenditure associated with abdominal pain was estimated to be $9.5 billion.[1] An analysis of ED visits for abdominal pain in the United Kingdom in 2017–2018 indicated that over half were high utilizers of healthcare, particularly those returning repeatedly with recurrent and unresolved abdominal pain.[2] Patients with recurrent abdominal pain and their repeat visits to EDs reflect a substantial unmet clinical need.[3,4]

Recurrent abdominal pain is defined as pain that persists for more than 3 months and occurs intermittently.[5] A typical workup may include a detailed history to understand the onset, duration, frequency, quality, and location of pain; physical examination; and laboratory tests including urinalysis, endoscopy, and imaging (which may include ultrasound, computed tomography [CT] scan, and/or magnetic resonance imaging).[6–9] Despite this comprehensive workup, findings may remain inconclusive; thus, exploratory surgical interventions are not uncommon.[3,4]

Recurrent abdominal pain is also a common reason for referral to a gastroenterologist.[6] For the gastroenterologist, the most important and informative part of the workup is taking a detailed history, as this is the aspect most likely to elicit clues for a particular disorder.[6] Awareness of these clues and assessing for red flags and alarm symptoms are essential. As recurrent abdominal pain is a hallmark symptom of a multitude of more common chronic conditions, uncommon diseases are often missed or not considered. Therefore, individuals with rare diseases often go undiagnosed for years while physicians who are not aware of these conditions offer evolving diagnoses in the face of new or progressing symptoms.[10]

It is not unusual for a physician to see an individual with a rare disease that has remained undiagnosed. Consequently, gastroenterologists should maintain an awareness of infrequent causes of abdominal pain and how they present differently from more common disorders. This may result in earlier diagnoses and more efficient management.[11]

Abbreviations used in this paper: **AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; ALA, aminolevulinic acid; ALAS, 5-aminolevulinic acid synthase; C, component; CAWP, chronic abdominal wall pain; CMI, chronic mesenteric ischemia; CT, computed tomography; CTA, computed tomography angiography; ED, emergency department; FMF, familial Mediterranean fever; GI, gastrointestinal; HAE, hereditary angioedema; HCP, hereditary coproporphyria; Ig, immunoglobulin; IL, interleukin; MALS, median arcuate ligament syndrome; MCAS, mast cell activation syndrome; MRA, magnetic resonance angiography; MVT, mesenteric venous thrombosis; PBG, porphobilinogen; SMVT, subacute mesenteric venous thrombosis; TPI, trigger point injection; VP, variegate porphyria.**

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With this in mind, we sought to improve awareness, symptom recognition, and differential diagnoses around uncommon but diagnosable causes of recurrent abdominal pain that may present to a gastroenterologist. Disease selection was based on expert opinion and on feedback from a group of community-based and academic gastroenterologists. The goal was to identify diseases or conditions characterized by recurrent abdominal pain that are seen infrequently but can be diagnosed with existing testing methods. Table 1 provides a summary of the key presenting symptoms and diagnostic tests for each disease or condition included in this review. This is not an exhaustive review of all infrequent, overlooked causes of recurrent abdominal pain. Authors in this field review the featured conditions in a concise manner, offering expert recommendations for recognition, diagnosis with existing physical examination and/or laboratory testing methods, and appropriate management strategies. These conditions should be considered when the initial diagnostic workup has failed, rather than as part of the initial differential diagnosis. Given that these are uncommon disorders that can be identified and treated in an outpatient setting, appropriate diagnosis has the likelihood to minimize recurrent ED visits and inpatient admissions. The aim is to provide gastroenterologists with the tools necessary to establish a timely and accurate diagnosis, which will optimize management and improve patient outcomes.

Chronic Abdominal Wall Pain

Disease Background

Chronic abdominal wall pain (CAWP), also known as anterior cutaneous nerve entrapment syndrome, is a common, yet often overlooked, cause of chronic abdominal pain.[12] CAWP may be the underlying etiology in 10%–30% of patients who present with undifferentiated abdominal pain in the outpatient setting.[13,14] Despite its prevalence, the diagnosis is often delayed and made only after patients have undergone extensive

Table 1. Overview of Rare Causes of Abdominal Pain

Condition	Key Presenting Symptoms	Key Diagnostic Test(s)
Chronic abdominal wall pain	Upper abdominal pain, typically focal and positional in nature[15]	Carnett's sign[12] Pinch test[19] Improvement following a TPI[12]
Vascular causes of recurrent abdominal pain		
Median arcuate ligament syndrome	Postprandial epigastric pain (up to 90% of patients)[49,50] Weight loss[49,50] Nausea[49,50] Vomiting[49,50] Diarrhea[49,50] Abdominal bruit that intensifies on deep expiration[49,50]	Traditional workup of abdominal pain[50] If negative: • CTA or MRA with deep expiratory phase[55] • DUS[56]
Splanchnic artery aneurysm	SpAAs[155-158] • Acute or chronic abdominal pain • Nausea • Malaise • GI bleeding CAA[159,160] • Abdominal pain • Nausea mimicking pancreatitis SMAA[159,160] • Chronic abdominal pain • Rupture	CT, MRI, or MRA[160] Abdominal ultrasound[160]
Chronic mesenteric ischemia	Abdominal discomfort or cramping occurring within 30 minutes of eating[51,52] Weight loss[32,54] Nausea[32,54] Vomiting[32,54] Diarrhea[32,54] Lower GI bleeding[32,54]	CTA[57,58] Mesenteric duplex ultrasound
Subacute mesenteric venous thrombosis	Nonspecific abdominal pain syndrome occurring in a "tumbleweed" pattern of relapsing and remitting pain[47]	CTA Magnetic resonance venography

Table 1. Continued

Condition	Key Presenting Symptoms	Key Diagnostic Test(s)
Allergic causes of recurrent abdominal pain		
Food allergy	Symptoms of allergy across multiple organ systems (including the skin, airway, and GI), occurring immediately after a culprit food[76]	Food-specific IgE testing in the blood and skin[80]
Mast cell activation syndrome	Symptoms of the skin, eg[77] • Flushing • Hives • Pruritus Symptoms of the airway, eg[77] • Throat scratching • Chest tightness • Rhinitis GI symptoms, eg[77] • Abdominal bloat and cramping • Abdominal pains	Baseline serum tryptase[161]
Angioedema	Swelling of the skin and mucosal surfaces Intestinal angioedema: • Crampy abdominal pain	Abdominal imaging (eg, CT scan) during period of symptoms[84]
Hereditary angioedema	Sudden-onset crampy and diffuse abdominal pain without other associated signs or symptoms[78]	Complement C4 test[78]
Acute hepatic porphyria	Severe nonfocal abdominal pain, typically associated with nausea, vomiting, and constipation[107] Neurologic symptoms[107]	Single spot urine test for ALA and PBG[119]
Familial Mediterranean fever	Fever[139] Serositis[139] Abdominal and/or chest pain[139] Arthralgias/arthritis[139] Erysipelas-like skin lesions[139]	As described in Table 3

ALA, aminolevulinic acid; CAA, coronary artery aneurysm; CT, computed tomography; CTA, computed tomography angiography; DUS, Doppler ultrasonography; GI, gastrointestinal; IgE, immunoglobulin E; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; PBG, porphobilinogen; SMAA, superior mesenteric artery aneurysm; SpAA, splenic artery aneurysm; TPI, trigger point injection.

laboratory, imaging, and procedural testing. This condition is more common in women than in men (ratio 4:1) and is also more common in those with obesity, other comorbidities related to pain syndromes, and depression.[15,16]

Pathophysiology

The pathogenesis of CAWP is thought to be related to entrapment of the cutaneous branches of thoracic nerves that pass through the rectus abdominis muscle.[17,18]

Clinical Features

The pain is typically focal, positional in nature, with the right upper quadrant being the most common site.[15] There may be associated allodynia or hyperalgesia. The diagnosis of CAWP requires a carefully elicited history and detailed physical examination.[12] The pain is often present over a prior surgical scar, although the absence of a scar does not rule out the condition.[12] It is typically localizable with one finger and may worsen with activities and actions that tense the abdominal muscles, such as bending, sitting, lying on the affected side, coughing, or sneezing.[12,19] When other features such as persistent vomiting, melena, sudden change in bowel pattern, or unintentional weight loss are present, they should prompt consideration of other organic or structural causes.[12]

Diagnosis

The presence of a positive Carnett's sign (Figure 1) on physical examination is highly suggestive of this condition. In the 2-step examination technique for detecting Carnett's sign, the clinician first identifies and palpates the area with maximal tenderness with the patient in the supine position (step 1).[12] The provider then asks the patient to raise both legs off the examination table or to bend the chin to touch the chest (step 2), in order to tense the abdominal muscles. The Carnett's sign is

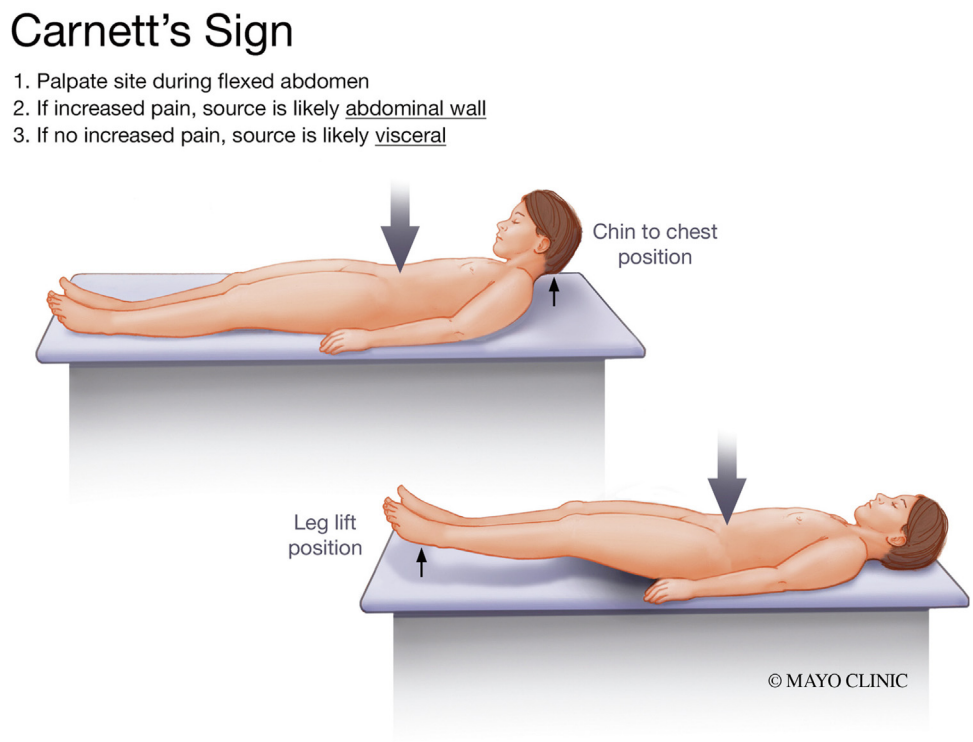

Figure 1. Carnett's sign is suggestive of chronic abdominal wall pain. From Amrit K. Kamboj, Patrick Hoversten, Amy S. Oxentenko, "Chronic abdominal wall pain: a common yet overlooked etiology of chronic abdominal pain," *Mayo Clinic Proceedings,* 2019, Volume 94, Number 1, pp. 139-144. Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.

considered positive if palpation of the abdomen in the location of usual tenderness in the tense position elicits worse pain compared with the rest position.[12] The pinch test, in which the clinician pinches the skin and subcutaneous tissue of the area with the maximal tenderness, can also be helpful.[19] A positive pinch test elicits disproportionate intense pain when pinching the area with abdominal tenderness (hyperalgesia), compared with the contralateral side, and is highly sensitive for CAWP.[19,20] In individuals in whom the diagnosis remains unclear despite the previous approach, improvement following a trigger point injection (TPI) can help to support the diagnosis.[12]

Management Options

The treatment of CAWP depends on the severity of symptoms and may include reassurance, activity modification, and pain relief with topical analgesics, neuromodulators, or TPI.[12] Patients should be educated that while symptoms from CAWP can be bothersome, they typically do not result in serious, long-term health complications. Additionally, vigorous activities that tense the abdominal muscles (ie, abdominal exercises) and can exacerbate the pain should be avoided. For those with mild symptoms, topical treatment with lidocaine patch application may suffice. While some patients may find a heating pad placed in the area of pain to be therapeutic, others find application of ice packs brings similar relief, so this should be tailored to personal preference. For those with moderate–severe symptoms, pain relief may be best achieved with a TPI, with or without ultrasound guidance, that utilizes an anesthetic agent (ie, lidocaine) with or without a glucocorticoid (ie, betamethasone or triamcinolone) administered to the area of maximal pain.[12,16,21–23] Pain relief with lidocaine can start a few hours after administration; however, the glucocorticoid can take several days to take effect. While some patients may have long-lasting improvement after a single TPI, others may require multiple TPIs (repeated no sooner than 3 months) in the event of incomplete initial response or recurrence of symptoms after complete initial response.[23,24] For gastroenterologists who are uncomfortable performing these injections, they can often be performed in a more specialized setting (ie, by a pain specialist). In patients who fail to respond to these interventions, other diagnoses of chronic abdominal pain should be entertained. Chemical neurolysis or surgical neurectomy may be considered in patients with truly refractory symptoms despite multiple TPIs who are felt to have a diagnosis consistent with CAWP.[25,26]

Vascular Causes Of Recurrent Abdominal Pain

Disease Background

Although vascular disorders affecting the small and large intestine usually cause acute abdominal pain, they also may result in abdominal pain that is recurrent or chronic. Vascular disorders causing recurrent or chronic

abdominal pain include median arcuate ligament syndrome (MALS), chronic mesenteric ischemia (CMI), and subacute mesenteric venous thrombosis (SMVT). Splanchnic artery aneurysms can also cause chronic abdominal pain. Due to frequent misdiagnoses, the true incidence and prevalence of these entities are unknown.

MALS, also known as celiac artery compression syndrome, refers to chronic postprandial abdominal pain associated with compression of the celiac artery by the median arcuate ligament of the diaphragm. Over time, the designation of MALS as an entity has been debated, and currently there is no universally accepted definition.[27,28] MALS occurs most frequently in women (4:1 ratio), particularly those who are thin and middle-aged.[29]

CMI is a rare condition accounting for <5% of all ischemic disorders of the intestine.[30] A recent prospective study conducted in the Netherlands found the incidence of CMI to be 9.2 per 100,000 inhabitants, with atherosclerotic CMI being the most common cause (7.2 per 100,000), followed by MALS (1.3 per 100,000) and chronic nonocclusive mesenteric ischemia (0.6 per 100,000), indicating that CMI is far more common than previously thought.[31] CMI occurs more frequently in women (12.0 per 100,000) than in men (6.5 per 100,000), and the incidence increases with age.[31] The diagnosis of CMI is difficult to confirm, with previous studies revealing an average of 10–15 months from symptom onset to diagnosis.[32,33]

MVT can occur as an acute, subacute, or chronic disorder. SMVT typically presents as recurrent abdominal pain over a period of weeks to months, without intestinal infarction.[34] The incidence of MVT overall has been reported to range from 2.0 to 2.7 per 100,000 person-years, 24%–40% of which are chronic MVT. The highest incidence occurs in individuals 70–79 years of age with an incidence of 11.3 per 100,000 person-years[35]; however, the exact incidence of SMVT has not been determined.[35–37]

Pathophysiology

While the exact pathophysiology of abdominal vascular disorders varies based on the condition (eg, atherosclerosis for CMI, hypercoagulable conditions for SMVT), the underlying mechanism involves decreased blood flow into or out of the intestine. The pathophysiology of MALS is unknown, but possibilities include ischemia from diaphragmatic compression of the celiac artery and pain due to a pulsating pressure on the celiac ganglion itself.[29,38]

CMI, or intestinal angina, is the result of transient episodes of inadequate intestinal blood flow leading to recurrent symptoms, thought to be provoked by the increased metabolic demands associated with digestion.[39] CMI is most often the result of mesenteric atherosclerosis, and can also result from vasculitis,[40] MALS, or fibromuscular dysplasia, or may be seen in the absence of anatomic causes of vascular obstruction, such as the low-flow states (nonocclusive mesenteric ischemia) accompanying heart failure, chronic obstructive pulmonary disease, or chronic kidney disease.[41,42] Mesenteric artery stenosis occurs in 18%–29% of the elderly population,[43–45] although only a minority will develop CMI because of the numerous collaterals that maintain intestinal blood flow. Most patients with symptomatic CMI have atherosclerotic involvement of at least 2 vessels (91%) and, in cases of single-vessel disease, >70% vessel stenosis is present, usually in the celiac artery (86%).[46]

SMVT is thought to be caused by hypercoagulability, stagnation of blood flow, and endothelial damage, which can affect the duodenum (4%–8% of MVT), jejunum (50%–81%), or the ileum (64%–83%).[34,47] SMVT typically occurs when there is venous occlusion causing ischemia, but enough collateral vessels to allow for recovery.[48] The portal, superior mesenteric, and splenic veins are most frequently involved; subacute inferior mesenteric vein thrombosis is rare.[34]

Clinical Features

Abdominal pain from vascular causes vary and can be either chronic or recurrent, based on etiology.

Clinical features of MALS typically include postprandial epigastric pain (up to 90% of patients), weight loss, nausea, vomiting, diarrhea, and an abdominal bruit that intensifies on deep expiration.[49,50]

The classic presentation of CMI is abdominal discomfort or cramping that occurs within 30 minutes of eating and resolves slowly over 1–4 hours.[51,52] Abdominal pain is often initially mild and progressively worsens over weeks to months.[53] Weight loss is a frequent sign of CMI as individuals develop sitophobia (fear of eating) because they associate pain with eating.[51,52] Early in the disease course, pain occurs after meals, but over time it begins to occur earlier in the meal, last longer, and eventually can become continuous; continuous pain indicates impending or actual intestinal infarction.[41,42] Almost all individuals with CMI present with abdominal pain, of which 74%–100% is postprandial.[51] Other clinical findings include weight loss (61%–78%, mean loss of 10.4 ± 5.4 kg), nausea and vomiting (13%), diarrhea (7%–13%), and lower GI bleeding (8%).[32,54] The triad of postprandial abdominal pain, weight loss, and the presence of an abdominal bruit is uncommon (22% of patients).[54] Physical examination is typically unremarkable, as the abdomen is usually soft and nontender, even during painful episodes.[52] An abdominal bruit is of limited diagnostic value, especially in thin persons.[51,52] Patients may appear cachectic due to ongoing weight loss.

SMVT often presents with a nonspecific "tumbleweed" pain pattern, characterized by its relapsing,

remitting nature, most likely due to recurrent thromboses and the development of collateral vessels.[47]

Diagnosis

MALS is a diagnosis of exclusion as celiac artery compression is nonspecific, and its clinical presentation is similar to other entities. Initial evaluation should include a traditional workup for abdominal pain, including esophagogastroduodenoscopy, right upper quadrant ultrasound, and CT abdomen and pelvis.[50,55] If this evaluation is negative, MALS should be considered and CT angiography (CTA) or a magnetic resonance angiogram (MRA) performed, including filming with the patient in deep expiration. In deep expiration, the diaphragm descends more than the celiac artery, and so focal narrowing of the celiac artery with a characteristic hooking will be pronounced and differentiate the stenosis in MALS from that of typical atherosclerosis.[50,55] Duplex ultrasound with inspiratory and expiratory measurements can also be considered.[56]

Due to the lack of specific diagnostic testing, CMI usually is diagnosed based on clinical presentation and radiologic testing, along with the exclusion of other disorders. The imaging modality of choice to evaluate for CMI is CTA, which has a sensitivity of 96% and specificity of 94% in diagnosing mesenteric vascular occlusion.[57,58] CTA is also helpful in ruling out other causes of chronic abdominal pain. MRA has the benefit of no radiation exposure, but in small studies has been shown to be less accurate than CTA.[59] While mesenteric angiography has been the gold standard for evaluation of the intestinal vasculature, its role is more limited today because of the use of CTA. Duplex ultrasonography has been shown to be sensitive and specific in identifying occlusion of the mesenteric vasculature, but it is operator-dependent and less accurate than CTA.[60,61] High-grade stenosis ($\geq$70% occlusion) in 2 or more of the major mesenteric vessels is typically diagnostic of CMI.[31] Endoscopic evaluation is appropriate to rule out other causes of abdominal pain but typically will reveal only nonspecific findings, such as erythema (42%) or edema (35%), which have little diagnostic value.[54,62] Functional testing, including visible light spectroscopy and gastric tonometry exercise testing, has been developed to more accurately diagnose CMI. Functional duplex ultrasonography, in which an ultrasound study of portal vein flow is performed in the fasting and the postprandial states after a standard test meal, is easy and reliably assesses the ability of mesenteric blood flow to increase after eating a standardized meal.[63] Laboratory testing has limited utility to diagnose CMI, but postprandial serum D-dimer and lactate levels are significantly elevated in patients with CMI.[64]

In SMVT, physical examination and laboratory tests are most often normal. Diagnosis requires a high index of suspicion and is usually made on CTA or magnetic resonance venography. CTA is the imaging modality of choice and has a high sensitivity (93%) and specificity (100%) for MVT. Magnetic resonance venography has been shown to be highly accurate as well.[65,66] Occlusion of the mesenteric veins with compensation via collateral vessels is typically diagnostic of SMVT.[67]

Management Options

Operative management of MALS is indicated in symptomatic patients with confirmed celiac artery compression on imaging. Surgical options for division of the MAL include open and laparoscopic (standard or robotic) approaches, with celiac ganglionectomy often performed concurrently.[50] In a systematic review of 400 patients that compared laparoscopic and open approaches, patients that underwent laparoscopic intervention were more likely to have immediate relief of symptoms (96% vs 78%), albeit with similar incidence of late recurrence of symptoms (5.7% vs 6.8%).[68] CT or endoscopic ultrasound–guided celiac ganglion blockade with local anesthetic agents or ethanol can be used to identify patients who may respond well to surgery, or can be used in highly select cases for long-term management.

Treatment of CMI includes surgical or endovascular revascularization. A large meta-analysis found significantly fewer postoperative complications (relative risk, 2.19) and a trend toward improved 30-day mortality (relative risk, 1.57) with an endovascular revascularization but fewer symptom recurrences and increased 3-year survival with surgical revascularization.[69] A recent guideline determined that reducing short-term mortality and morbidity with endovascular revascularization outweighs the long-term benefits of surgical revascularization and recommended endovascular intervention for most patients.[51] In patients who are younger with longer life expectancy, surgery should be considered first-line therapy given its superior long-term outcomes. Overall, endovascular and surgical revascularizations are successful in 85%–100% and 97%–100% of cases, respectively.[61] Immediate symptom relief is reported in 87%–95% of patients with endovascular and 90%–98% of patients with surgical interventions, with relief maintained at 5 years in 51% of endovascular and 89%–92% of surgically revascularized patients.[70]

Treatment of SMVT is generally conservative, with the initiation of systemic anticoagulation for 3–6 months to prevent further extension of the thrombus and allow for recanalization.[39,71] Surgical exploration is reserved for patients with signs of bowel infarction.[72] Due to its infrequent diagnosis, morbidity and mortality data are lacking in patients with SMVT.

Allergic causes of recurrent abdominal pain

Disease Background

Allergy and allergic-type conditions may frequently present with abdominal pain. In patients with recurrent

abdominal pain, it is important to consider whether they have an allergic profile and whether allergic-type symptoms may coexist. Allergic diseases and syndromes need to be considered if the patient has a history and/or family history of atopy, including eczema, allergic rhinitis, and asthma.

Pathophysiology

The clinical manifestations of immunoglobulin E (IgE)–mediated allergy result from the crosslinking of a specific allergen (eg, peanut) with the corresponding IgE antibody on the surface of mast cells. In the GI tract, exposure of a specific food allergen in a sensitized individual results in degranulation of the resident mast cells and release of functional mediators such as tryptase.[73] Various triggers may also inappropriately activate mast cells through non-IgE mechanisms to give rise to a clinical syndrome affecting multiple organs systems, including the GI tract.[74] Angioedema is an allergic disorder that results in swelling of various tissues, including the mucosal surface of the intestine, and is mediated by histamine, bradykinin, or an idiopathic, hereditary cause. Hereditary angioedema (HAE) most commonly results from a deficient or defective component 1 (C1) inhibitor, a serine protease with several substrates including the kinin-generating pathways.[75] Insufficient C1 inhibitor leads to overproduction of the vasodilator bradykinin and unopposed breakdown of C4 in the complement pathway.

Clinical Features

A spectrum of presenting signs and symptoms can indicate an allergic cause of abdominal pain. Allergic GI symptoms may include abdominal pain, which is usually diffuse and crampy, as well as bloating, nausea, and loose stools. Allergic patients can often point to a particular food or environmental trigger that induces symptoms. Predisposed patients may have high incidences of IgE-mediated food allergies,[73] with predictable symptoms occurring immediately after ingestion of a culprit food and resolving within a day. The most common food allergens in adults are shellfish, tree nuts, and peanuts.[76]

An allergic-type, non–IgE-mediated syndrome that may be considered as a cause of recurrent abdominal pain is mast cell activation syndrome (MCAS).[77] The defining features of MCAS include skin-associated (eg, flushing [Figure 2], hives, pruritus), airway-associated (eg, throat scratching, chest tightness, rhinitis), and GI-associated (eg, abdominal bloat and cramping abdominal pain) symptoms.[77] It is important to note that abdominal pain will not occur in isolation and coexists with the skin or other mast cell activation manifestations. These symptoms occur after exposure to predictable triggers,[77] are intermittent, and have a variable duration that may last hours to days. Classic triggers for MCAS include alcohol, certain foods (eg, gluten, processed foods containing dyes and chemicals), medications (eg, antibiotics), and strong smells (eg, fragrances and cleaning products).[77]

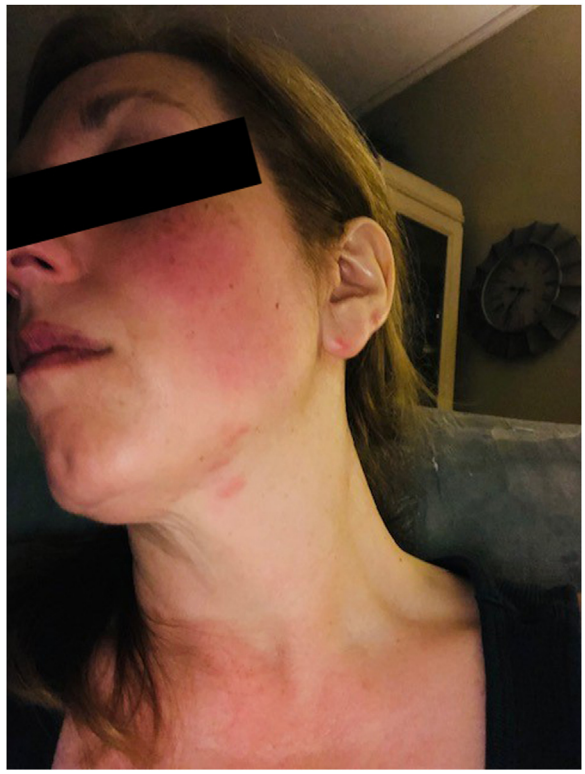

Figure 2. Flushing associated with MCAS. Image provided by Matthew J. Hamilton.

Another acute onset abdominal pain condition recognized in the allergic patient is angioedema. This characteristically presents with swelling of the skin (typically face, limbs, trunk) and mucosal surfaces including the GI tract.[78] Patients with intestinal angioedema classically present with crampy abdominal pain that may be associated with nausea, abdominal distension, and diarrhea.[78] The severity of pain is variable but may be severe enough to prompt ED visits and unnecessary surgeries when not properly recognized.[79] As with the other allergic disorders, the associated presenting symptoms and triggers for symptoms are important in determining the underlying cause. Patients presenting with hives and pruritus are likely experiencing histamine-induced angioedema as part of an allergic reaction, while patients taking nonsteroidal anti-inflammatory drugs or angiotensin-converting enzyme inhibitors may have bradykinin-induced intestinal angioedema.

Patients with HAE present with sudden onset and crampy and diffuse abdominal pain (that may last for several days) without other associated signs or symptoms, such as hives, and without a history of obvious exposure.

Diagnosis

Food allergies are identified by food-specific IgE blood and skin testing.[80]

If the diagnosis of MCAS is suspected, supporting laboratory studies include a baseline serum tryptase.[81] If this level is >20 ng/mL, further workup for systemic mastocytosis is indicated.[82] A tryptase level >8 ng/mL suggests hereditary alpha-tryptasemia, a newly described disorder that has symptom overlap with MCAS.[83] For MCAS, tryptase should be repeated immediately after a severe reaction (within 2–6 hours). A level that is at least 20% plus 2 ng/mL of baseline is considered positive for mast cell activation.[81] Patients should also complete a 24-hour urine collection when symptomatic to test for elevated levels of metabolites of mast cell mediators including histamine (N-methylhistamine), prostaglandin (prostaglandin-F2 alpha or D2), and leukotriene (leukotriene-E4).

For angioedema, abdominal imaging (eg, CT scan) when active symptoms are present may reveal characteristic features, such as a segment of bowel with straightening, wall thickening, and mild dilation.[84] However, these features are not always present, and the history and physical examination may be the only diagnostic clues.

HAE is a challenging diagnosis and should be considered in those in whom physical examination, laboratory testing, and abdominal imaging is normal. Key historical clues include a history of angioedema of the skin or other mucosal surface; 50% of patients with HAE will experience an episode of life-threatening laryngeal edema.[75] Inheritance is autosomal dominant, and therefore patients will have a family history of angioedema. If the diagnosis of HAE is suspected based on any of these features, the screening laboratory test of choice is a complement C4 test. Patients with the common forms of HAE will have low C4 levels, typically <50% of normal, a finding that is observed even when the patient is asymptomatic. In a patient with suspected HAE based on history, physical examination, and low C4 level, the C1 inhibitor level and function can be tested next to confirm the diagnosis and to determine the subtype of HAE.

Management Options

In individuals with food-mediated allergies, strict avoidance of culprit foods will prevent episodes, but patients are required to have a nonexpired epinephrine pen available at all times.

The diagnosis of MCAS is further supported by clinical response to medications that block mast cells and mast cell mediators.[85] As a first pass, it is reasonable to trial a nonsedating H1 antihistamine (eg, cetirizine, loratadine) at the onset of symptoms. If the patient experiences a degree of relief, mast cell stabilizing medications can be added and titrated based on symptom response (Figure 3). Abdominal pain and GI symptoms of MCAS are readily treatable using this approach, and therefore other causes for symptoms need to be considered if the patient remains symptomatic.

It is recommended that patients diagnosed with HAE be referred to a specialist (often allergy/immunology specialty) because very specific treatments are required. Although it is still reasonable to trial antihistamines such as intravenous diphenhydramine in the acute setting in a patient with suspected angioedema, these medications will not help, and treatments such as recombinant C1 inhibitor or bradykinin antagonists are needed.[86]

Acute hepatic porphyria

Disease Background

Porphyrias are inherited disorders of the heme biosynthesis pathway. Heme is synthesized through 8 enzymatic steps, and mutations that lead to reduced activity in these enzymes result in the 8 inherited porphyrias.[87,88] Symptoms of the porphyrias are due to the specific intermediates that accumulate prior to the defective enzymatic step. There are 4 acute hepatic porphyrias (AHP): acute intermittent porphyria (AIP);

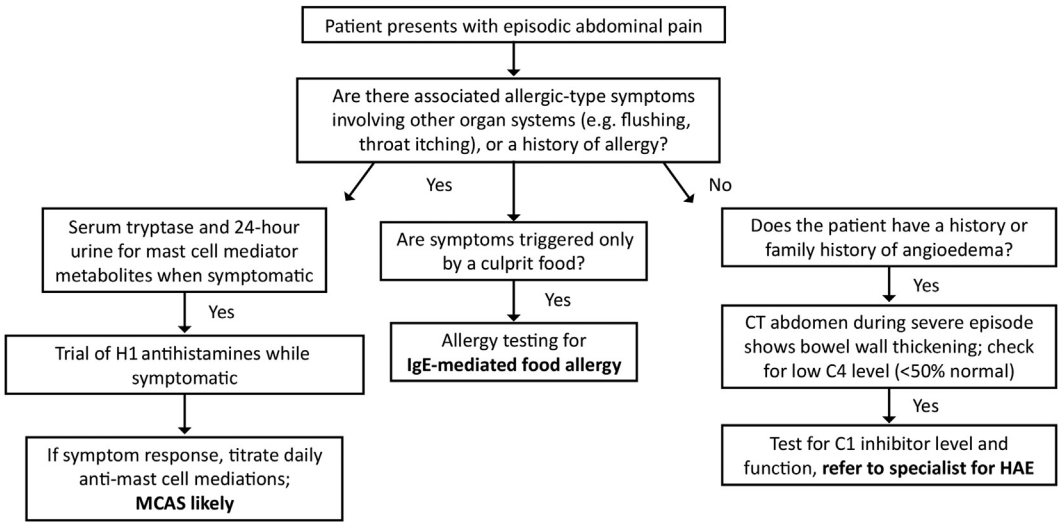

Figure 3. Diagnostic algorithm for abdominal pain in the allergic patient.

variegate porphyria (VP); hereditary coproporphyria (HCP); and 5-aminolevulinic acid (ALA) dehydratase deficiency porphyria (Table 2). Approximately 90% of symptomatic AHP patients are women in their reproductive years, and the most common presentation is episodic, severe abdominal pain. AHPs are often missed as a diagnosis in patients presenting with severe abdominal pain, with the average time from onset of symptomatic AHP to diagnosis being 15 years.[89] Fortunately, acute porphyria attacks can be diagnosed with a simple urine test that is sensitive and specific, and effective treatments are available.

Pathophysiology

Heme is predominantly formed by erythroblasts in the bone marrow (75%–80%) and hepatocytes in the liver (15%–20%).[88] The pathway is controlled by the first and rate-limiting enzyme, 5-ALA synthase (ALAS). In nonerythroid cells, including hepatocytes, ALAS1 is expressed and is subject to feedback regulation by heme.[88,90,91] In the AHPs, ALAS1 remains the rate-limiting step in the liver, even with a partially defective enzyme downstream. Under conditions of increased hepatic heme demand, ALAS1 expression increases, and the defective enzymatic step becomes the rate-limiting step. This results in abnormal accumulation of ALA and porphobilinogen (PBG), as well as insufficient heme production, which further activates ALAS1. This creates the metabolic setting for an acute attack.

Porphyrin precursors, in particular ALA, are neurotoxins, whereas porphyrins are light-absorbing chemicals that act as photosensitizers, resulting in skin damage. Acute attacks are always accompanied by elevated urine ALA, and effective therapy correlates with decreased ALA levels.[92]

AIP, HCP, and VP are autosomal dominant disorders while 5-ALA dehydratase deficiency porphyria is a very rare autosomal recessive disorder (with fewer than 10 cases reported worldwide).[93–97] Disease-causing mutations in AHP genes result in at least 50% reduction of the activity in the corresponding enzyme. While all AHPs are rare diseases, the prevalence of the genetic carrier state for AHPs is between 1:1300 and 1:1785, which is much higher than previously thought.[98,99] The vast majority of genetic carriers of AHP do not experience symptomatic acute attacks in their lifetime. The estimated penetrance of symptomatic disease is ~1% of AIP gene carriers[99] with HCP and VP thought to be more often latent than AIP.[100] These patients have normal ALA and PBG levels and are not clinically affected by this disease.

The low penetrance indicates the likely presence of additional factors that are required for symptomatic manifestation of AHPs.[101,102] Sex hormones, particularly progesterone, are known to precipitate attacks. Other common precipitating factors include medications and chemicals that induce cytochrome P450 enzymes in the liver, acute illness such as infection, stress, excess alcohol intake, and caloric deprivation. These factors all induce hepatocyte ALAS1 messenger RNA expression.[103–106]

Clinical Features

All 4 AHPs present with identical clinical symptoms of episodic, severe neurovisceral attacks due to abnormal accumulation of the porphyrin precursors ALA and

Table 2. Overview of Acute Hepatic Porphyrias

	ADP	AIP	HCP	VP
Enzyme (gene)	ALA-dehydratase (*ALAD*)[87]	Hydroxymethylbilane synthase (*HMBS*)[87]	Coproporphyrinogen oxidase (*CPOX*)[87]	Protoporphyrinogen oxidase (*PPOX*)[87]
Estimated prevalence	8 reported cases[162]	~1 in 20,000[95]	~1 in 500,000[163]	~1 in 300,000[163]
Clinical pearls	Rarest of the acute porphyrias; biochemically shows elevated ALA with normal PBG[163]	Most common form of acute hepatic porphyria[95]	Can present with both acute attacks and blistering skin lesions[163]	Can present with both acute attacks and blistering skin lesions[163]; high prevalence in South Africa due to founder effect from a Dutch settler[163]
Urinary PBG[88]	Normal or slightly increased	Increased	Increased	Increased
Urinary ALA[88]	Increased	Increased	Increased	Increased
Second-line testing[88]	Urinary porphyrin: increased COPRO III Fecal porphyrins: normal or slightly increased	Urinary porphyrin: increased URO, COPRO III Fecal porphyrins: normal or slightly increased	Urinary porphyrin: increased URO, COPRO III Fecal porphyrins: increased COPRO III	Urinary porphyrin: increased URO, COPRO III Plasma porphyrins: peak at 626 nm Fecal porphyrins: increased PROTO, COPRO III

ADP, ALA-dehydratase deficiency porphyria; AIP, acute intermittent porphyria; ALA, aminolevulinic acid; COPRO, coproporphyrin; HCP, hereditary coproporphyria; PBG, porphobilinogen; PROTO, protoporphyrin; URO, uroporphyrin; VP, variegate porphyria.

PBG.[107] In VP and HCP, both porphyrin precursors and porphyrins accumulate, and patients with these types can present with both neurovisceral attacks and cutaneous symptoms. During an acute attack, 95% of patients present with severe nonfocal abdominal pain, typically associated with nausea, vomiting, and constipation. Neurologic symptoms are present in up to 70% of acute attacks.[107] All divisions of the nervous system can be affected,[108,109] and the wide range and nonspecific nature of the symptoms contributes to the difficulty in diagnosing acute porphyria attacks. The rate of symptom progression is variable, but can be rapid, progressing to flaccid tetraplegia and respiratory paralysis within days. Prolonged or frequent attacks can lead to permanent neurologic damage, neuropathy, and chronic pain.[110]

The vast majority of symptomatic AHP patients experience only one or a few acute attacks in their lifetime. These attacks are often precipitated by triggers, and outside of acute attacks, these patients have normal ALA and PBG levels. An estimated 3%–5% of symptomatic AHP patients experience recurrent attacks, typically defined as having more than 4 attacks per year. These attacks are usually not associated with identifiable triggers. More than 50% of those who experience frequent recurrent attacks have chronic neurologic symptoms, and 35% have a diagnosis of neuropathy.[110,111] These individuals have markedly impaired quality of life[112,113] and are at higher risk for long-term complications of AHP, including liver disease, hepatocellular carcinoma,[114] and chronic renal failure.[115,116] ALA and PBG levels in those with frequent recurrent attacks are elevated, even between attacks.[117]

Diagnosis

The key to diagnosis is measurement of ALA, PBG, and creatinine in a single spot urine sample collected during or within a few days of an acute attack (Table 2). Levels of ALA and/or PBG expressed as per gram or per millimole of creatinine in the urine that are >4 times the upper limit of normal and level of urine PBG that exceeds 10 mg/g creatinine establish the diagnosis of AHP.[118] After an acute attack of AIP, urinary ALA and PBG can remain elevated for weeks to months.[119] Genetic testing is used for confirmation of the gene involved and the exact mutation, but is not recommended as a first-line diagnostic test due to the low penetrance of symptomatic disease.

Management Options

The primary goals of treatment during an acute attack are to relieve ALAS1 induction in the liver, leading to decreased production of ALA, and symptomatic management of the severe pain. Identifiable precipitating factors, such as medications that induce cytochrome P450s, should be stopped.[104] Carbohydrate loading is commonly used during early stages of acute attacks because prolonged fasting induces the expression of peroxisome proliferator-activated receptor gamma coactivator 1-alpha, which induces the expression of ALAS1.[104,120]

Definitive treatment for acute attacks is intravenous heme infusions.[92,121–124] Heme rapidly downregulates ALAS1 expression in the liver, thus stopping the continued accumulation of ALA and PBG. Symptomatic relief depends on elimination of excess ALA and PBG and typically takes 48–72 hours. The recovery rate of neurologic symptoms can vary depending on the underlying pathology. Timely treatment with heme results in normalization of ALA and PBG levels, improvement of attack symptoms, and avoidance of long-term neurologic symptoms.

Recently, a novel small interfering RNA-based therapy against ALAS1 has been approved for prevention of acute attack in patients with frequent recurrent attacks.[125] Givosiran is an ALAS1-specific small interfering RNA that is administered subcutaneously as a monthly injection and taken up selectively by hepatocytes.[126] It effectively normalizes ALA levels and significantly reduces the number of acute attacks.

Familial Mediterranean fever

Disease Background

Familial Mediterranean fever (FMF) is the oldest described and most common of the autoinflammatory hereditary periodic fever syndromes. Characterized by recurrent attacks of fever and serosal inflammation, its origins are believed to date to early Mesopotamia.[127] Most commonly described in individuals of Mediterranean descent, genetic migration has led to the identification of FMF across the globe, and although epidemiological data are limited, more than 100,000 cases have been documented.[128] In the United States, FMF is identified predominately in Ashkenazi Jewish and Middle Eastern populations.[129]

FMF is more common in men (1.2:1) than in women and more than 90% of patients experience their first episode prior to 20 years of age. Onset after 40 years of age is rare and usually associated with milder disease.[130,131]

Pathophysiology

Historically described as an autosomal recessive disorder, the pathogenesis of FMF appears more complex. Classic FMF develops when mutations occur in the *MEFV* gene located on chromosome 16.[132] Over 300 mutations have been described; however, 5 (M694V, M680I, V726A, M694I, E148Q) account for more than 66% of identified cases.[132,133] M694V is considered the most pathogenic, and individuals homozygous recessive for this mutation

experience a more severe clinical course. However, 10%–20% of individuals meeting diagnostic criteria for FMF have no identifiable *MEFV* mutations, and up to 25% carry one or none of the known mutations.[134,135] This has led to an updated genetic hypothesis that the FMF phenotype may be inherited autosomal dominantly, or that penetrance and expressivity are influenced by other genetic or environmental factors.[136]

FMF is a disorder of the innate immune system. The *MEFV* gene encodes pyrin, a protein found in the cytoplasm of cells of myeloid lineage. Mutations in this gene result in gain-of-function alterations in pyrin, which, through a cascade of intermediary steps, result in inflammation mediated by interleukin (IL)-1, IL-18, and other chemotactic agents.[137,138]

Clinical Features

The clinical presentation of FMF is variable. Differences in symptoms experienced and frequency and severity of attacks are presumed secondary to variations in genetic and environmental triggers.[139] The variable nature of these episodes commonly leads to diagnostic delay. Typical attacks last between 1 and 4 days and remit spontaneously. Patients are symptom-free between attacks. Identified triggers include infections, surgery, menstruation, cold exposure, emotional stress, and vigorous exercise. Some experience prodromes inclusive of constitutional symptoms, mild discomfort at sites of inflammation, anxiety, and/or changes in taste or appetite.[140,141] Classic episodes are typically characterized by fever and serositis presenting as individual or combinations of symptoms, including abdominal and/or chest pain, arthralgias/arthritis, and erysipelas-like skin lesions.[139] Less common manifestations include myalgias,[139] pericarditis,[139] scrotal swelling,[127,142] headaches,[127,143] and aseptic meningitis.[127,139,144]

The most concerning long-term complication of FMF and cause of death is secondary AA amyloidosis.[145] Amyloid deposition occurs in the gastrointestinal tract, liver, spleen, heart, thyroid, and testes but is most commonly identified in the kidneys. Renal amyloidosis can present asymptomatically as proteinuria, nephrotic syndrome, or end-stage renal disease. GI manifestations are typically malabsorptive in nature.[141]

Diagnosis

The diagnosis of FMF is complex. The lack of understanding of the genetic basis of FMF has led to the development of diagnostic algorithms based on clinical criteria and responses to therapy. Genetic testing can be confirmatory. While multiple classifications have been proposed,[146,147] diagnostic criteria and algorithms advanced by Livneh et al[148] more than 2 decades ago remain the gold standard (Table 3).

Management Options

Recently, the European League Against Rheumatism published recommendations for the treatment of FMF.[149] The mainstay is colchicine. When provided prophylactically, colchicine negates the recurrence of FMF attacks in the majority of patients and prevents the development of secondary amyloidosis. It is not effective during active flares. Overall, approximately 60% of patients respond to daily colchicine, whereas 20%–30% and 5%–10% of patients experience partial or no response, respectively. For these individuals, adjunctive treatments with

Table 3. Diagnostic Criteria for FMF

Major Criteria (Typical Attacks)[a]	Minor Criteria (Incomplete Attacks)[b]	Supportive Criteria
1. Peritonitis (generalized) 2. Pleuritis (unilateral) or pericarditis 3. Monoarthritis (hip, knee, ankle) 4. Isolated fevers	1. Abdomen 2. Chest 3. Joint 4. Exertional leg pain 5. Positive response to colchicine	1. Family history FMF 2. Appropriate ethnic origin 3. Age <20 years at onset 4. Attacks severe requiring bedrest 5. Attacks spontaneously remit 6. Symptom-free between attacks 7. Transient elevations in WBC, ESR, SAA, and/or fibrinogen 8. Episodic proteinuria/hematuria 9. Negative laparotomy or removal of healthy appendix 10. Parental consanguinity

The following criteria should be met to make an accurate diagnosis of FMF: ≥1 major criteria; or ≥2 minor criteria; or 1 minor plus 5 supportive criteria; or 1 minor criterion plus ≥4 of the first 5 supportive criteria.
Adapted with permission from Livneh et al.[148]
ESR, erythrocyte sedimentation rate; FMF, familial Mediterranean fever; SAA, serum amyloid A; WBC, white blood cell.
[a]Typical attacks defined as ≥3 of the same type, febrile (temperature ≥38°C), short (lasting 12 hours to 3 days).
[b]Incomplete attacks are defined as attacks that differ from typical attacks by 1 or 2 features: temperature ≥38°C; attacks are longer or shorter than a typical attack but not <6 hours or >7 days; no signs of peritonitis identified during abdominal attacks; abdominal attacks are localized; arthritis involves joints other than the hip, knee, and ankle.

immunomodulators and biologic agents have been trialed with the most robust data supporting the addition of IL-1 inhibitors. Benefits from anti-tumor necrosis factor and anti-IL-6 agents have also been described in small case series/reports.[150,151]

Discussion

Timely recognition and accurate diagnosis of recurrent abdominal pain is crucial to avoid unnecessary pain and suffering by patients and to implement effective treatment. The consequences of under-recognition and misdiagnosis include unnecessary surgery[3,4,11,152] and testing,[14] repeated hospitalizations,[153] increasing frequency of attacks,[153] delays in effective treatment leading to disease progression or life-threatening complications,[11,118,152,153] the use of the wrong treatments with resultant side effects,[152,154] and even death.[11,152,153]

Given the nonspecific nature of abdominal pain as a symptom and the multitude of more common chronic conditions that may cause it, timely diagnosis is impeded by lack of consideration, lack of awareness, and the inability to recognize some of the rarer or overlooked causes of recurrent abdominal pain. When other healthcare professionals cannot identify the cause of abdominal pain, the gastroenterologist is sought to solve the clinical conundrum. Therefore, gastroenterologists must be familiar with both common and rare causes of abdominal pain and consider various rare potential etiologies in their differential diagnosis.[11,118]

With these expert recommendations, gastroenterologists have the knowledge and tools needed to consider 5 of the key rare or overlooked causes of recurrent abdominal pain, and the opportunity to change a patient's disease course.

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