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Review article: diagnostic and therapeutic approach to persistent abdominal pain beyond irritable bowel syndrome

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Summary

Background: Persistent abdominal pain (PAP) poses substantial challenges to patients, physicians and healthcare systems. The possible aetiologies of PAP vary widely across organ systems, which leads to extensive and repetitive diagnostic testing that often fails to provide satisfactory answers. As a result, widely recognised functional disorders of the gut–brain interaction, such as irritable bowel syndrome and functional dyspepsia, are often diagnosed in patients with PAP. However, there are a number of less well-known differential diagnoses that deserve consideration.

Aim: To provide a comprehensive update on causes of PAP that are relatively rare in occurrence.

Methods: A literature review on the diagnosis and management of some less well-known causes of PAP.

Results: Specific algorithms for the diagnostic work-up of PAP do not exist. Instead, appropriate investigations tailored to patient medical history and physical examination findings should be made on a case-by-case basis. After a definitive diagnosis has been reached, some causes of PAP can be effectively treated using established approaches. Other causes are more complex and may benefit from a multidisciplinary approach involving gastroenterologists, pain specialists, psychologists and physiotherapists. This list is inclusive but not exhaustive of all the rare or less well-known diseases potentially associated with PAP.

Conclusions: Persistent abdominal pain (PAP) is a challenging condition to diagnose and treat. Many patients undergo repeated diagnostic testing and treatment, including surgery, without achieving symptom relief. Increasing physician awareness of the various causes of PAP, especially of rare diseases that are less well known, may improve patient outcomes.

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1 | INTRODUCTION

Although there is no commonly accepted definition, persistent abdominal pain (PAP) is considered continuous or intermittent abdominal discomfort that persists for at least 6 months and fails to respond to conventional therapeutic approaches.[1] This condition is frequently encountered by primary care clinicians, gastroenterologists and pain management specialists. Epidemiological data suggest that prevalence of PAP is 22.9 per 1000 person-years and is similar regardless of age group, ethnicity or geographical region.[1] In a recent survey of over 10,000 individuals, 81% reported experiencing abdominal pain in the past week, 60% reported pain onset within the past 5 years and nearly 40% reported pain onset more than 5 years prior.[2]

Aetiologies vary widely because PAP may arise from many different mechanisms throughout the body.[1] The cause of PAP can be classified as organic or functional. Organic aetiologies have clearly identified anatomical, physiological or metabolic causes, whereas functional aetiologies do not despite a thorough diagnostic evaluation. The association of gastrointestinal symptoms and dysfunction with psychological factors supports a gut–brain interaction.[3] The Rome IV classification of functional gastrointestinal disorders is based primarily on symptoms related to motility disturbance, visceral hypersensitivity and altered central nervous system processing. The aetiology of PAP may also be based on its origin as follows: (1) originating from abdominal viscera, (2) referred from an extra-abdominal source, (3) genetic origin and (4) centrally mediated disorders.

Diagnosis and management of PAP are challenging and frustrating for patients and physicians due to the poor sensitivity of patient medical history and physical examination, an inconclusive or negative diagnostic work-up and the need for a broad differential diagnosis. Clinicians not only need to recognise somatic abnormalities, but they must also perceive the patient's cognitions and emotions related to the pain.[4] By taking adequate time to listen to the patient and perceive psychological factors, clinicians can offer reassurances and suggest behavioural changes, prevent somatic fixations and increase patient satisfaction.[5]

The most frequent reasons for consulting the gastroenterologist, irritable bowel syndrome (IBS)[6] and functional dyspepsia[7] are the most widely recognised gastrointestinal diseases associated with PAP. These disorders impose a considerable burden on healthcare systems,[8] associated with substantial healthcare costs and productivity loss due to high rates of absenteeism.[1] Other widely recognised gastrointestinal diseases associated with PAP include inflammatory bowel diseases, chronic pancreatitis and gallstones. The current review provides a comprehensive update on the diagnosis and management of some less well-known causes of PAP.

2 | DIAGNOSTIC APPROACH

The diagnosis of PAP is based on patient medical history, physical examination, psychological assessment and objective diagnostic tests.[9,10] Given its chronicity, many patients will have already undergone extensive and redundant medical testing. Any change in the description of PAP or emergence of new symptoms should alert the physician to an acute-on-chronic condition (e.g., perforation, obstruction, abscess in the presence of confirmed gastrointestinal disease) or a new condition that warrants investigation (e.g., cancer development). This is especially true as patients age because many gastrointestinal conditions have a peak incidence before the age of 60 years.[1] Other 'red flag' symptoms include fever, vomiting, diarrhoea, acute change in bowel habit, obstipation, syncope, tachycardia, hypotension, concomitant chest or back pain, unintentional weight loss, night sweats and acute gastrointestinal bleeding.

Key information to be obtained during an initial consultation with a patient with PAP should help discern whether the pain origin is organic or functional (Figure 1).[11,12] Organic pain is frequently described using sensory terms such as cramping, burning or stabbing, whereas functional pain has been described using 'emotional' terms such as 'felt too sick to go to work'.[13] Organic pain usually occurs in a more systemic manner according to better-defined nerve regions and fluctuates more widely in intensity. A logistic regression analysis identified several criteria that discriminated between organic disease and IBS.[14] Age older than 50 years and rectal bleeding were strongly linked to PAP associated with an organic aetiology. Female sex and pain on six or more occasions in the previous year, radiating beyond the abdomen or associated with looser bowel motions, were associated with an IBS diagnosis.

An attempt must be made to identify a triggering event, such as an adverse life event, infection, initiating a new medication or surgical procedure.[11] The patient's diet is an important consideration. Recently it has been demonstrated that gastrointestinal symptoms of diarrhoea, constipation, bloating and/or abdominal pain may be associated with an intolerance to fermentable oligo-, di- and monosaccharides and polyols (FODMAPs).[15] These short-chain carbohydrates are poorly absorbed in the small intestine and may induce abdominal pain and bloating. Also, symptoms may be triggered by specific nutrients—for instance, in case of true food allergies—or by histamine-rich nutrients.

Patients with PAP often undergo repetitive diagnostic tests and try various therapies with poor or no clinical benefit. Despite the time-consuming nature, it is important to entirely review all information, along with digestive surgical history, to minimise additional testing.[9,11,16] Patients with disorders of the gut–brain interaction associated with PAP (e.g., IBS) are at an increased risk of undergoing unjustified surgical procedures,[17] such as cholecystectomy (odds ratio [OR], 2.09; 95% confidence interval [CI], 1.87–2.29), appendectomy (OR, 1.45; 95% CI, 1.33–1.56), hysterectomy (OR, 1.70; 95% CI, 1.55–1.87) and back surgery (OR, 1.22; 95% CI, 1.05–1.43).[18]

While recommendations regarding evaluation of chronic abdominal pain have been published,[19] specific algorithms for the diagnostic work-up of PAP do not exist. Instead, appropriate investigations tailored to patient medical history and physical examination findings should be made on a case-by-case basis. Many patients with PAP have repeated standard laboratory testing,

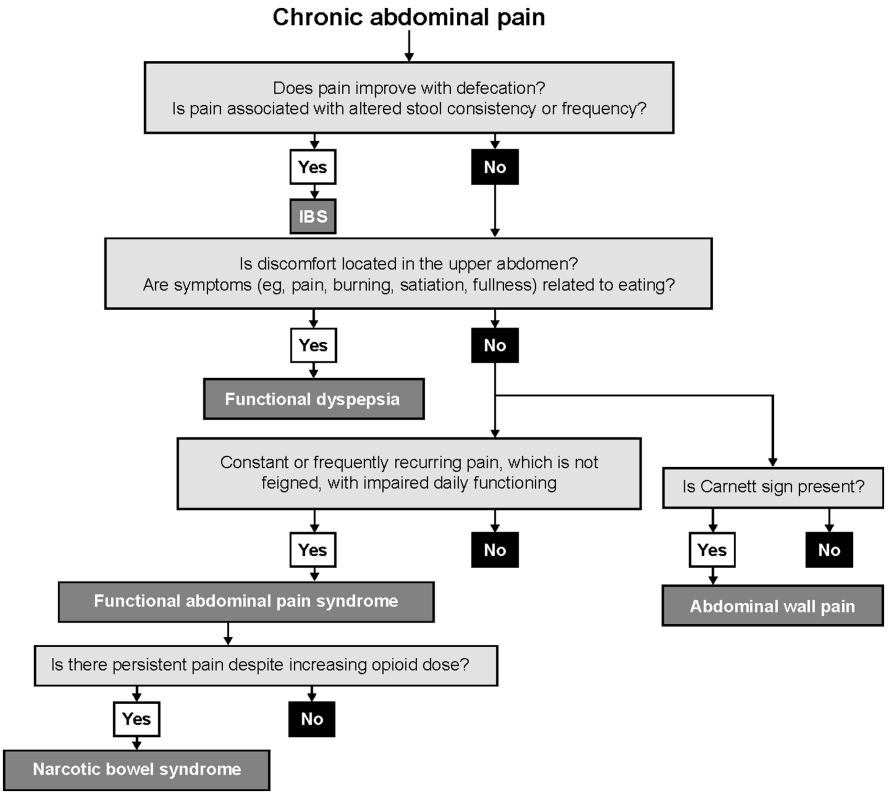

FIGURE 1 Diagnostic algorithm for disorders of gut–brain interaction associated with persistent abdominal pain. IBS, irritable bowel syndrome. Reprinted from Mayo Clinic Proceedings, vol. 91, no. 8, Bharucha et al[12] Copyright 2016, with permission from Mayo Foundation for Medical Education and Research.

upper and lower endoscopic examinations, abdominal ultrasounds and computed tomography (CT) scans of the abdominal/pelvic area. In the absence of alarm features, any additional tests should be ordered in a conservative and cost-effective manner. After excluding common organic aetiologies, some additional clinical situations should be considered before determining a diagnosis of PAP associated with a gut–brain disorder. Overall, patients with PAP who are referred to tertiary centres can be approached with three steps: (1) question the patient at length regarding symptoms and medical history; (2) summarise all previous investigations and treatments and whether they were effective; (3) from the first two steps, deduce the relevant complementary explorations to be performed. Several differential diagnoses are discussed below and summarised in Table 1.[1,3,11,12,20–70] This list is inclusive but not exhaustive of all of the rare or less well-known diseases potentially associated with PAP.

3 | PAP LINKED TO A DIGESTIVE DISORDER

3.1 | Eosinophilic gastroenteritis

Eosinophilic gastroenteritis (EGE) is a chronic inflammatory disorder characterised by eosinophilic infiltration in the stomach and intestine.[20] The estimated prevalence in the United States ranges from 8.4 to 28 cases per 100,000 individuals and is expected to rise with the increasing understanding of the disorder. Occurring at any age, with peaks between the third and fifth decade of life, typical symptoms include abdominal pain accompanied by nausea, vomiting, dyspepsia, diarrhoea and malabsorption.

The pathophysiology of EGE is not fully understood.[20] Hypersensitivity plays a major role, as many patients have a history of seasonal allergies, food sensitivities, asthma and eczema. Both immunoglobulin E (IgE)-dependent and delayed T-helper type 2 cell–mediated hypersensitivity mechanisms are involved in EGE pathogenesis. Laboratory results, radiological findings and endoscopy can help confirm an EGE diagnosis, but it is diagnosed via histological examination of gastric and duodenal biopsies describing an eosinophilic infiltration.[20] A specific count of eosinophils per high-power field is required as eosinophil count varies based on age, environmental factors and the anatomic location in the gastrointestinal tract (normal levels in the duodenum: <10 eosinophils per high-power field in children and <19 in adults; caecum: ≤40 eosinophils/high-power field; colon: ≤16 in children and ≤50 in adults).[20]

The management of EGE includes dietary modification and pharmacological approaches.[20] Corticosteroids are the mainstay of EGE therapy. Alternative therapies for intolerance or corticosteroid resistance include mast cell stabilisers, leukotriene-receptor antagonists, antihistamines, immunomodulators and biological agents targeting interleukin-5, tumour necrosis factor α and IgE.

3.2 | Mesenteric panniculitis

Typically occurring in late adult life, mesenteric panniculitis is a fibroinflammatory condition of unknown aetiology,[21] often found incidentally in patients undergoing cross-sectional CT scan for

TABLE 1 Disorders associated with persistent abdominal pain

Disease	Prevalence	Distinguishing features	Additional signs/symptoms
Persistent abdominal pain linked to a digestive disorder			
Eosinophilic gastroenteritis[20]	8.4–28.0 cases per 100,000	Persistent abdominal pain	Diarrhoea, dyspepsia, nausea and vomiting, atopia, allergy
Mesenteric panniculitis[21]	NA	Abdominal discomfort, fever, nausea, vomiting, diarrhoea, constipation	Extensive fibrosis may lead to intestinal obstruction and vascular compression
Chronic mesenteric ischaemia[22–25]	1 in 1000 hospital admissions	Postprandial abdominal pain, weight loss, food aversion, epigastric bruit	Abdominal discomfort, nausea, vomiting, diarrhoea or constipation, diffuse atherosclerosis
Median arcuate ligament syndrome[26]	NA	Epigastric pain and tenderness, nausea, vomiting, weight loss and postprandial or exercise-induced abdominal pain, abdominal bruits	NA
Postoperative adhesions[1,27–29]	45%–90% of patients with persistent abdominal pain	Persistent abdominal pain	Past history of one or several abdominal/gynaecological surgeries open or celio
Sphincter of Oddi dysfunction[30,31]	1.5% of general population	Pain localised to the right upper quadrant or epigastrium lasting 30 min or more, biliary pain	NA
Pain of gynaecological origin			
Endometriosis[64–66]	7%–10% of women	Chronic abdominal pain, chronic pelvic pain, dyspareunia, dysmenorrhoea, infertility	NA
Chronic abdominal wall pain			
Anterior cutaneous nerve entrapment syndrome[32–35]	5%–67% of patients referred to specialists	Severe pain in right upper quadrant with a focal area of ≤2 cm in diameter, positive Carnett sign, exacerbated by movement	NA
Abdominal muscle pain[11,33,35]	NA	Persistent abdominal pain exacerbated by sedentary lifestyle	NA
Abdominal wall hernia[32,33]	NA	Palpable mass, increased size during coughing, reduced size in supine position	NA
Referred osteoarticular pain			
Pain of spinal origin[11,32,33,70]	NA	Radicular symptoms in dermatomal or myotomal distribution, localised spinal and paraspinal tenderness and myelopathy in severe cases; aggravated by physical activity	Manifestations related to vertebral osteoarticular damage
Pain of costal origin[32,33]	NA	Pain in upper abdomen or chest along lower rib margin, pain may be positional, clicking sound	NA
Abdominal pain of systemic origin			
Adrenal insufficiency[36,37]	Primary: 15–22 per 100,000 (Nordic countries), 10 per 100,000 (other European countries), 0.4 per 100,000 (South Korea) Secondary: 14–28 per 100,000 (Spain, United Kingdom)	Abdominal pain, unintentional weight loss, anorexia, postural hypotension, profound fatigue, muscle pain, hyponatraemia	Skin hyperpigmentation, salt cravings, hyponatremia

Pathophysiology	Diagnosis	Treatment
IgE-dependent and delayed Th2 cell-mediated hypersensitivity	Eosinophilic infiltration in gastric and duodenal specimens	Corticosteroids, mast cell stabilisers, leukotriene antagonists, antihistamines, immune modulators and biological agents
Unknown aetiology, possible causes include autoimmune processes and low-grade inflammation-stimulating fibrogenic factors	Often found incidentally on computed tomography scan	Immuno-modulators, tamoxifen, progesterone, surgery for extensive fibrosis and bowel obstruction
Atherosclerotic stenosis of one or more mesenteric arteries; less frequently caused by vasculitis	Clinical symptoms, computed tomography angiography, functional test	Smoking cessation, antiplatelet therapy, revascularization
Celiac artery compression by the median arcuate ligament	Exclusion of alternative causes of abdominal pain	Surgical median arcuate ligament release and celiac ganglionectomy
Caused by manipulation of internal organs during surgery	Exploratory surgery	Laparoscopic adhesiolysis is not recommended
Aberrant sphincter physiology leading to increased resistance to bile outflow and subsequent rise in intrabiliary pressure, altered sphincter dynamics	Criteria for biliary pain, elevated liver enzymes or dilated bile duct, but not both	Medications to reduce basal sphincter pressures in sphincter of Oddi, medications to inhibit sphincter motility, possible endoscopic sphincterotomy
Retrograde menstruation is the most widely accepted pathogenesis	Palpation of pelvic and abdominal area, combined with patient's history; magnetic resonance imaging	Gonadotropin-releasing hormone agonists, aromatase inhibitors, oral contraceptive pills, nonsteroidal anti-inflammatory drugs and opioids; surgical removal of endometrial lesions
Anterior cutaneous nerve entrapment syndrome results from entrapment of an anterior cutaneous branch of a thoracic nerve at the lateral border of the rectus abdominis muscle	Response to a trigger point injection of local anaesthetic	Lidocaine patches and trigger point injections (corticosteroid, local anaesthetic or combination) Chemical neurolysis or surgical neurectomy for severe, refractory pain
Result of microtrauma, repeated tension or poor posture	Abnormal or asymmetric muscle tone, specific pain points and antalgic posture	Physical therapy
Herniation develops in a natural or iatrogenic weak spot in the abdominal wall	Physical examination with patient standing and supine, ultrasonography or computed tomography for subtle hernias	Surgery (open or laparoscopic) for enlarging or painful hernias
Irritation of the intercostal nerves in the anterior abdominal wall by spinal processes	Physical examination, imaging tests and nerve conduction studies in severe cases	Nonsteroidal anti-inflammatory agents, muscle relaxants, nerve blocks
Occurs when cartilage on lower ribs becomes displaced and irritates the intercostal nerves	Hooking manoeuvre: clinician hooks fingers under costal margin and pulls upward (pain or clicking indicates a positive result)	Surgery (costal cartilage excision) for persistent or severe pain
Deficient production or action of glucocorticoids, with or without deficiency in mineralocorticoids and adrenal androgens	Paired assay of serum cortisol and adrenocorticotropic hormone indicating low cortisol concentration and adrenocorticotropic hormone concentration twice the upper reference limit	Glucocorticoid, mineralocorticoid, adrenal androgen replacement

TABLE 1 (Continued)

Disease	Prevalence	Distinguishing features	Additional signs/symptoms
Mast cell activation syndrome[38–41]	Up to 17% of general population	Acute urticaria, flushing, abdominal cramping/pain, diarrhoea, hypotensive syncope or near syncope and tachycardia	Headache, nausea, non-specific gastrointestinal complaints and life-threatening anaphylaxis Intolerance to multiple foods with histamine-rich nutrients
Systemic mastocytosis[42–44]	1 in 7700 to 1 in 10,400	Persistent abdominal pain	Diarrhoea
Hereditary angiooedema: C1 esterase deficiency[67–69]	1 in 10,000 to 1 in 50,000	Oedema of skin, abdominal pain attacks (acute and chronic), life-threatening laryngeal oedema	Vomiting, nausea, diarrhoea, intestinal obstruction
Persistent abdominal pain of genetic origin[a]			
Acute hepatic porphyria[45–49]	1 in 1700 (acute intermittent porphyria)	Severe, diffuse abdominal pain lasting several days	Nausea, vomiting, abdominal distention, diarrhoea, constipation, hyponatraemia, neurological symptoms
Lead poisoning[50,51,a]	NA	Symptoms similar to those caused by acute hepatic porphyria	Vomiting, constipation, and anorexia; nervous, haematological, and renal impairment, contaminated water consumption
Ehlers–Danlos syndrome[52–54]	1 in 150,000 (vascular Ehlers–Danlos syndrome)	Persistent abdominal pain	Various gastrointestinal complications Familial history Join hypermobility Skin elasticity
Low phospholipid-associated cholelithiasis syndrome[55]	1% of symptomatic cholelithiasis; nearly three times more common in women; occurs in young adults with low or normal body weight	Typical biliary pain with recurrent symptoms after cholecystectomy	Serious complications: pancreatitis, acute cholangitis, intrahepatic lithiasis Familial history, cholecystectomy in young age
Familial Mediterranean fever[56–58]	1 in 200 to 1 in 1000 in populations of Eastern Mediterranean descent	Intense and diffuse abdominal pain that may last several days; recurrent flares of fever associated with polyserositis	Tender and tympanic abdomen Familial history Geographical and ethnical origins
Dysautonomia and centrally mediated disorders of persistent abdominal pain			
Postural orthostatic tachycardia syndrome[59,60]	500,000 to 3 million (United States)	Severe orthostatic symptoms	Urinary and gastrointestinal symptoms (e.g., chronic abdominal pain, bloating, constipation, dyspeptic symptoms)
Narcotic bowel syndrome[12,61,62]	~5% of patients who receive opioid therapy	Severe to very severe abdominal pain in presence of escalating or continuous opioid therapy	Bloating, constipation, nausea, and vomiting
Centrally mediated abdominal pain syndrome[3,12,63]	0.5%–1.7%	Severe abdominal pain; no relationship to eating or bowel movements; impaired daily functioning	NA

Abbreviations: IgE, immunoglobulin E; MDR3, multidrug resistance; NA, not available; Th2, T-helper cell, type 2.

[a]Included because of pathophysiology and symptoms similar to those of acute hepatic porphyria.

Pathophysiology	Diagnosis	Treatment
IgE-dependent allergic inflammation	Clinical symptoms, often with hypotension, trigger-related substantial increase in serum tryptase levels and response of clinical symptoms to mast cell–stabilising drugs or drugs counteracting the effects of mast cell–derived mediators	Trigger identification and avoidance, antihistamines, leukotriene receptor antagonists, mast cell stabilisers, monoclonal antibodies
Somatic *KIT* gene mutations result in increased production of mast cells and inflammation	Mast cells in extracutaneous organs, atypical mast cell morphology, *KIT* gene mutation, elevated serum tryptase concentrations	Antihistamines, corticosteroids, interferon-α and *KIT* tyrosine kinase inhibitors; allogeneic stem cell transplantation for life-threatening disease
Type 1: deficiency in quantity of functional C1 esterase inhibitor produced Type 2: dysfunctional C1 esterase inhibitor	Evaluation of patient and family history; review of medications; physical examination with imaging and laboratory tests	Acute attacks: C1 esterase inhibitors Prophylaxis: attenuated androgens or C1 esterase inhibitors
Haeme biosynthesis enzyme deficiency results in accumulation of neurotoxic haeme precursors, delta-aminolevulinic acid and porphobilinogen Autosomal dominant inheritance	Elevated concentrations of delta-aminolevulinic acid and porphobilinogen in urine and plasma	Intravenous human hemin, givosiran, liver transplantation in severe cases
Haeme biosynthesis enzyme deficiency	Lead concentrations in blood	Chelation therapy
COL3A1 gene mutation (vascular Ehlers–Danlos syndrome) results in type III collagen deficiency	Clinical signs, non-invasive imaging, and detection of genetic mutation	Symptomatic treatment Appropriate precautions during surgery
Mutation of *ABCB4* gene that encodes MDR3 protein, reducing biliary phosphatidylcholine concentration and precipitating gallstones	Two of the following criteria: age at onset <40 years; symptom recurrence after cholecystectomy; hyperechogenic intrahepatic foci on ultrasound	Ursodeoxycholic acid
MEFV gene mutations result in increased interleukin-1β production and inflammation Autosomal recessive inheritance	Clinical findings; detection of *MEFV* gene mutations	Colchicine Interleukin-1β inhibitors (colchicine resistance or intolerance)
Visceral hypersensitivity, central sensitisation, somatic hypervigilance, and behavioural amplification	Endoscopic, radiographic, and motility tests	Gastrointestinal symptoms are managed by treating the most prominent symptoms and may include the use of antiemetics, carbidopa, pyridostigmine, tricyclic antidepressants, or other combinations of gut-directed and central agents
Opioid-induced, centrally mediated, visceral hyperalgesia	Based on concurrent symptoms and opioid use	Patient education, opioid detoxification, antidepressants or anxiolytics, psychological interventions
Dysregulation of the gut–brain interaction results in central sensitisation and disinhibition of pain signals	Diagnosed using Rome IV criteria	Patient education, behavioural and psychological interventions, pharmacotherapy (generally tricyclic antidepressants), multidisciplinary pain rehabilitation programme

various indications including abdominal pain. Mesenteric panniculitis usually involves the small bowel and appendix; patients may present with abdominal discomfort, fever, nausea, vomiting, diarrhoea and constipation. In patients with extensive fibrosis, shortening and compression of the mesentery and its vessels may occur, leading to intestinal obstruction and vascular compression. However, as mesenteric panniculitis might be found incidentally, it is always important to reanalyse symptoms before attributing them to panniculitis. The pathogenic events suggest a low-grade inflammation in which preadipocytes are more likely to convert over time to macrophages. Increased secretion of proinflammatory adipocytokines initiate and maintain inflammatory changes and are followed by the release of fibrogenic factors, such as transforming growth factor, activating fibroblasts and collagen deposition.

Treatment is not codified, primarily using immunomodulators: corticosteroids, colchicine, azathioprine and cyclophosphamide, as well as tamoxifen and progesterone.[21] Patients with extensive fibrosis and bowel obstruction should undergo surgical resection or debulking.

3.3 | Chronic mesenteric ischaemia

Chronic mesenteric ischaemia (CMI) is defined as insufficient blood flow through the splanchnic vessels to the gastrointestinal tract, primarily arising from atherosclerotic stenosis of one or more mesenteric arteries for a duration of at least 3 months.[22,25] CMI is caused by occlusive or nonocclusive mesenteric ischaemia.[24] While mesenteric artery stenosis occurs in up to 10% of people older than 65 years, CMI has a low incidence overall and accounts for less than one in 1000 hospital admissions for abdominal pain.[23] The prevalence of occlusive and nonocclusive ischaemia is unknown.[24] Postprandial abdominal pain, weight loss and epigastric bruit compose what is referred to as the 'classic triad' of CMI.[22,24,25] Abdominal pain with postprandial worsening, starting 10–30 min after a meal and lasting 1–2 h, is present in 74%–100% of patients with CMI.[24] Diagnosis of CMI is based on clinical symptoms, radiological evaluation of mesenteric vasculature and functional assessment of mucosal ischaemia, if available,[22,25] but remains a challenge because of a differential diagnosis that includes chronic pancreatitis, celiac disease, duodenal ulcers, abdominal malignancies and IBS.[24] Thus, patients should be evaluated for potential CMI by a multidisciplinary expert panel comprising a gastroenterologist, interventional radiologist and vascular surgeon for compatibility of history, presence of significant mesenteric artery stenosis on imaging, absence of an alternative diagnosis and, if available, results of a functional test, when being evaluated for potential CMI.[24,25]

Management of asymptomatic CMI is performed conservatively with smoking cessation and antiplatelet therapy.[23] Symptomatic patients with occlusive CMI are treated with revascularization to alleviate symptoms, improve quality of life, restore normal weight and prevent bowel infarction to improve survival.[23,25]

3.4 | Median arcuate ligament syndrome

Median arcuate ligament syndrome (MALS) is described by a variety of clinical signs and symptoms, including abdominal pain.[26] MALS is associated with celiac artery compression by the median arcuate ligament (a fibrous arch uniting the diaphragmatic crura).[26] However, the pathophysiology of MALS is poorly understood, and patients have variable presentations with differing severity and response to treatment.[26] Due to the lack of universal diagnostic criteria, the diagnosis of MALS remains one of exclusion (excluding more common, alternative causes of abdominal pain).[26] Management of MALS aims to address the hypothesised mechanism through decompression of MAL-associated constriction of the celiac artery, with or without celiac ganglionectomy to target the neuropathy component of pain.[26] There are insufficient long-term (>5 years) follow-up data on the efficacy of surgery for treatment of MALS, and a consensus on the optimal surgical approach is lacking.[26]

3.5 | Postoperative adhesions

Surgical procedures may contribute to PAP if postsurgical abdominal adhesions develop.[1] Risk factors for adhesion formation include open surgery (vs minimally invasive), use of foreign bodies (mesh) and presence of a contaminated surgical field. However, the incidence of adhesions varies widely in the literature (45%–100%), and causal relationships to abdominal pain have been difficult to prove. No non-invasive tests are available to diagnose abdominal adhesions, but most are identified during exploratory surgery.[27,28] Laparoscopic adhesiolysis has been proposed as a treatment for PAP.[28] A systemic review of 25 studies found a positive outcome of adhesiolysis on pain relief, but because the studies lacked controls, these results are hardly discussed.[27] However, the only randomised study comparing adhesiolysis to a sham procedure in patients with chronic abdominal pain demonstrated no beneficial effect of adhesiolysis after 1-year follow-up,[71] and after 12 years of follow-up, patients with adhesiolysis had more pain, more surgery and more consultations.[29] Based on these results, adhesiolysis cannot be recommended.

3.6 | Sphincter of Oddi dysfunction

Sphincter of Oddi dysfunction is a complicated cause of PAP. It is characterised by symptoms of biliary and/or pancreatic obstruction without identifiable mechanical causes.[31] The Rome IV diagnostic criteria include the intensity of pain, justifying emergency room visits and nocturnal awakenings.[30] Cholecystectomy is a predisposing factor, and the diagnosis is made either by endoscopic retrograde cholangiopancreatography and manometry or by hepatobiliary scintigraphy.[30,31] Elevated liver enzymes may also be present.[31] Sphincter of Oddi dysfunction can be classified into three types based on the presence of biliary obstruction.[31] Conservative management is recommended initially due to the risks involved

with invasive approaches.[30] To reduce basal sphincter pressures in sphincter of Oddi dysfunction, nifedipine, phosphodiesterase type-5 inhibitors, trimebutine, hyoscine, butylbromide, octreotide and nitric oxide have been utilised.[30] Agents to inhibit sphincter motility include H2 antagonists, gabexate mesylate, ulinastatin and gastrokinetic agents.[30] There is consensus that patients with definite evidence for biliary obstruction should be treated with endoscopic sphincterotomy without manometry.[30] However, therapeutic response to sphincterotomy may vary between types.[31]

4 | PAIN OF GYNAECOLOGICAL ORIGIN: ENDOMETRIOSIS

Endometriosis is a chronic inflammatory disease of gynaecological origin that primarily affects women in their reproductive years. The estimated prevalence ranges from 7% to 10% of women.[64,65] Among the theories proposed, the most widely accepted is that retrograde menstruation is associated with the pathogenesis of endometriosis.[64] In endometriosis, uterine endometrial cells migrate into the pelvic cavity and form lesions on multiple organs.[64,66] Endometriosis is typically characterised by chronic pelvic pain, dyspareunia, dysmenorrhoea and infertility.[64,65] Furthermore, women with endometriosis often experience gastrointestinal symptoms, such as chronic abdominal pain.[64–66] Diagnosis can begin with a clinical examination involving palpation of the pelvic and abdominal area combined with an assessment of the patient's medical history.[64] During the last decades, transvaginal ultrasound and magnetic resonance imaging emerged as diagnostic tools, making diagnosis easier.[64] However, small lesions may exist below these techniques' detection thresholds.[64] In these cases, evolution of symptoms under treatment could be an argument for a positive diagnosis. Pharmacological and surgical treatment options are available and should be managed by a specialist in this area.[64,66] Pharmacological options to modulate hormonal signalling, reduce inflammation or treat pain include use of gonadotropin-releasing hormone agonists, aromatase inhibitors, oral contraceptive pills, nonsteroidal anti-inflammatory drugs and opioids.[64] Surgical treatment involves the removal of endometrial lesions, but a surgical approach can be challenging and may require multiple interventions.

5 | CHRONIC ABDOMINAL WALL PAIN

Chronic abdominal wall pain is a common but under-recognised cause of PAP, easily mistaken for a visceral disorder or IBS, and in some cases it can be associated with IBS.[33,72,73] The prevalence of chronic abdominal wall pain in the general population is unknown, but the specialists to whom patients are referred estimate it at 5%–67%.[33] Up to 30% of PAP cases with negative work-up can be attributed to chronic abdominal wall pain.[32] The aetiology varies depending on which component of the abdominal wall is affected, but it can often be related to trauma, scar tissue formation or increased pain after sporting activities. In these situations, diagnosis is mainly clinical and treatment is empiric, as there are no randomised clinical studies reported.

5.1 | Anterior cutaneous nerve entrapment syndrome

The most frequent cause of chronic abdominal wall pain is anterior cutaneous nerve entrapment syndrome (ACNES), occurring when an anterior cutaneous branch of a thoracic nerve at the lateral border of the rectus abdominis muscle is entrapped.[32,33] Intra- or extra-abdominal pressure (e.g., herniation, tissue oedema, fibrosis) or scar formation may cause traction of the nerve, leading to nerve irritation and potentially nerve ischaemia.[33,35]

Characteristic features of ACNES include constant or mildly fluctuating severe pain, located most commonly in the right upper quadrant and increased when abdominal muscles are tensed (positive Carnett sign and variations with postural changes).[32,33] An examiner uses the Carnett test to identify the area of tenderness by palpating the abdomen of a supine patient and then applying continuous pressure as the patient contracts abdominal muscles and raises their head and trunk or lower extremities off the table. When the muscles are tensed, the patient is asked if the pain is altered. A positive Carnett sign is a stable or worsening pain at the point of maximal tenderness during contraction. Overall, pain is commonly characterised as sharp and can be pointed out with a fingertip by the patient.[74,75] ACNES is more common in women aged between 30 and 50 years and with various predisposing conditions such as obesity, pregnancy, prior abdominal surgery and sports-related injuries.[32,73] Medical history and physical examination are central to an accurate diagnosis of ACNES, which is supported by a positive Carnett sign and confirmed by an immediate response to a point injection of local anaesthetic. Physical examination is a relatively reliable and simple way to make the diagnosis, which markedly reduces medical costs and avoids repeating diagnostic tests.[73] No specific diagnostic tests are available, and a positive response to treatment is probably the only indicator that can be used to confirm the diagnosis. Treatment includes conservative measures, lidocaine patch applications, trigger point injections (corticosteroid, local anaesthetic or combination) and in severe refractory cases, chemical neurolysis or surgical neurectomy.[34,35]

5.2 | Abdominal muscle pain

PAP may also arise from microtrauma, repeated tension or poor posture, possibly exacerbated by a sedentary lifestyle.[11,33] Clinical diagnosis is based on the presence of abnormal/asymmetric muscle tone, specific pain points and antalgic posture, which is an unnatural position assumed by an individual to minimise or alleviate pain or discomfort (e.g., patient leaning on the painful side). Physical therapy

may be helpful in increasing the strength, mobility and flexibility of abdominal muscles to reduce pain intensity.[35]

5.3 | Abdominal wall hernia

Herniation localised to a natural or iatrogenic weak spot on the abdominal wall is a classic cause of PAP.[32,33] Hernias (epigastric, hypogastric, umbilical, inguinal, incisional and Spigelian) are characterised by a palpable mass or fullness that requires a diligent physical examination performed with the patient standing and supine.[32,33] Hernias usually decrease in size when the patient is supine. Conversely, hernia bulging is elicited by coughing. Ultrasonography or CT allows for the detection of subtle hernias (epigastric, incisional and Spigelian). Spigelian hernias are at high risk for strangulation because of their smaller size and may require surgical intervention. Enlarging or painful hernias require surgical repair to relieve discomfort and prevent complications.[33]

6 | REFERRED OSTEOARTICULAR PAIN

6.1 | Pain of spinal origin

Often described in diabetic patients, thoracic spinal radiculopathy may manifest as referred abdominal pain due to irritation of the intercostal nerves in the anterior abdominal wall by spinal processes.[32,76] Narrowing of the space where nerve roots exit the spine, due to stenosis, bone spurs, disc herniation or other conditions, may result in radiculopathy. Thoracic spinal radiculopathy is characterised by radicular symptoms with a dermatomal or myotomal distribution, localised spinal and paraspinal tenderness and, in severe cases, myelopathy symptoms.[33]

Thoracic spinal radiculopathy is typically diagnosed via physical examination (delicately pinching subcutaneous tissues at the level of emerging spinal roots), imaging tests and, in some cases, nerve conduction studies.[32,33] Symptoms can be increased by physical activity[11] and are often managed with conservative approaches (physical therapy, nonsteroidal anti-inflammatory agents, muscle relaxants and nerve blocks with anaesthetic agents and/or corticosteroids).[76]

6.2 | Pain of costal origin

Slipping rib syndrome (Cyriax syndrome) is characterised by pain in the upper abdomen or chest along the lower rib margin.[32] This syndrome occurs when cartilage on the lower ribs becomes displaced, entrapping and irritating the intercostal nerves. Pain may be positional: a clicking, cracking sound or sensation may occur as the ribs move relative to each other. Slipping rib syndrome is diagnosed using a hooking manoeuvre in which the clinician hooks their fingers under the costal margin and pulls upward; a positive result is indicated by pain or clicking. Usually it can be managed conservatively, but if the condition persists or causes severe pain, costal cartilage excision may be considered.[33]

7 | ABDOMINAL PAIN OF SYSTEMIC ORIGIN

7.1 | Adrenal insufficiency

Adrenal insufficiency can be divided into primary (adrenal), secondary (pituitary) and tertiary (hypothalamic) forms.[36] It can manifest at any age, but usually presents in people between the ages of 20 and 50 years.[36] Abdominal pain is one of the main clinical symptoms of adrenal insufficiency among other symptoms such as weakness, fatigue, anorexia, weight loss orthostatic hypotension and salt craving.[37] The nonspecific digestive symptoms, such as abdominal pain, sometimes lead to misdiagnosis of an acute abdomen.[77] These digestive manifestations are thought to be a direct consequence of glucocorticoid and mineralocorticoid deficiency, but the mechanism remains unclear.[77] In a cross-sectional controlled study of 119 patients with chronic adrenal insufficiency, 40% of the study population reported abdominal pain at least once a week during the previous 3 months.[77] Symptoms were consistent with the Rome IV IBS criteria in 30% of patients with chronic adrenal insufficiency, and IBS-like symptoms were significantly more frequent in patients with chronic adrenal insufficiency than in controls.[77] Assessment of adrenal insufficiency by cortisol measurement after tetracosactide is frequent in patients with inflammatory bowel disease after withdrawal of steroid therapy, and this diagnosis should be considered in case of abdominal pain in these patients.[78]

Adrenal insufficiency is primarily diagnosed by the standard-dose corticotropin test, and prolonged stimulation with exogenous corticotropin is used to differentiate between primary and secondary or tertiary adrenal insufficiency.[37] As adrenal insufficiency is potentially life-threatening, treatment should be initiated as soon as the diagnosis is confirmed.[37] First-line treatment is glucocorticoid replacement, particularly with hydrocortisone.[37] Other therapeutic options include mineralocorticoid or adrenal androgen replacement.[37]

7.2 | Mast cell activation syndrome

Mast cell activation disease can be classified into systemic mastocytosis and mast cell activation syndrome (MCAS).[39] Systemic mastocytosis is a haematological disorder characterised by mast cell accumulation in various organs such as the liver, spleen, bone marrow and gastrointestinal tract[42] with both gastrointestinal and extra-gastrointestinal symptoms.[79] Gastrointestinal symptoms, mainly abdominal pain and diarrhoea, occur in 60%–80% of cases,[42] overlapping with those of functional abdominal disorders (IBS and functional dyspepsia) in which mast cells may

be upregulated.[79] Some foods may trigger symptoms.[80] The estimated prevalence of systemic mastocytosis ranges from one in 7700 to one in 10,400.[44]

Most cases (>80%) are caused by somatic mutations in the *KIT* gene, leading to overproduction of mast cells and an inflammatory response.[43] Diagnosis is based on criteria developed by the World Health Organization: one major and one minor criterion or three minor criteria must be met. The major criterion is >15 mast cells in an extracutaneous organ. Minor criteria include >25% of mast cells with atypical morphology (spindle-shaped, degranulated and/or multinucleated), *KIT* D816V mutation, CD2 and CD25 expression on CD117 mast cells and serum tryptase concentrations >20 ng/ml. Mast cell infiltrates are usually identified in the bone marrow.[81] Gastrointestinal biopsies can be negative for tryptase expression and may be increased in patients with other conditions, including IBS.[81]

Treatment of less advanced systemic mastocytosis focuses on trigger avoidance and symptom management using antihistamines, corticosteroids or disodium cromoglycate.[42,43] Treatment of advanced systemic mastocytosis involves antiproliferative agents, including interferon-α and cladribine, or targeted *KIT* tyrosine kinase inhibitors. Allogeneic stem cell transplantation is considered for young and fit patients with a suitable transplant donor.

MCAS is a chronic multisystem disease of abnormal mast cell activation that leads to allergic and inflammatory symptoms.[39] Diagnosis is based on the presence of typical clinical signs and symptoms of severe recurrent acute systemic mast cell activation involving at least two organ systems, laboratory-confirmed mast cell involvement and favourable response to drugs with mast cell-stabilising agents or acting against mast cell-derived mediators.[40,82] MCAS can be further classified based on aetiology as either primary (detection of *KIT*-mutated, clonal mast cells), secondary (detection of underlying IgE-dependent allergy or other reactive mast cell activation-triggering pathology) or idiopathic (absence of a triggering reactive state or *KIT*-mutated mast cells).[40,83] Gastrointestinal symptoms are common, with abdominal pain as one of the more frequently reported.[39] MCAS is often associated with hypermobile Ehlers–Danlos syndrome (hEDS) and postural orthostatic tachycardia syndrome (POTS), both of which exhibit extensive gastrointestinal involvement.[39] Very recently, some arguments suggest that MCAS is prevalent in patients with long-COVID.[84] Mast cell activation triggers include stress, food, alcohol, excipients in medications, infections, altered microbiome and environmental stimuli.[39]

Treatment of MCAS requires the identification and avoidance of triggers.[39] Patients treated pharmacologically are given medications, including non-sedating H1 and H2 histamine receptor antagonists, in a stepwise manner and monitored for benefit and reactions.[39] Over-the-counter options include vitamin C, vitamin D and quercetin.[39] Second-line therapy includes montelukast, a leukotriene receptor antagonist, and/or cromolyn sodium, a mast cell stabiliser.[39] Monoclonal antibodies such as omalizumab can also be considered later as pharmacological therapy.[39]

7.3 | Hereditary angiooedema: C1 Esterase inhibitor deficiency

Hereditary angiooedema results from mutations in the C1 esterase inhibitor gene, and can be classified into two types: type 1 is associated with a deficiency in the quantity of functional C1 esterase inhibitor produced; type 2 is associated with dysfunctional C1 esterase inhibitor.[67,68] The most common symptoms of hereditary angiooedema include oedema of the skin, abdominal pain attacks and life-threatening laryngeal oedema.[68] The abdominal pain can present as severe acute-onset abdominal pain (typically lasting 1–5 days) or as chronic recurrent abdominal pain, with up to 80% of patients with hereditary angiooedema experiencing recurrent abdominal pain.[67,68] Patients may experience these PAP symptoms without other hereditary angiooedema symptoms (cutaneous or respiratory oedema); thus, diagnosis may be difficult.[67]

Diagnosis is based on an evaluation of patient and family history and a review of medications to identify angiooedema triggers.[67] Additionally, during an acute episode, physical examination with imaging of the abdomen, and laboratory tests, can confirm a diagnosis.[67] Imaging results from CT, abdominal X-ray or abdominal ultrasonography may reveal intestinal wall and mucosal thickening, fluid accumulation in bowel loops, obstruction, or ascites, depending on the test.[67]

The management of hereditary angiooedema can include therapy for acute attacks (C1 esterase inhibitors) or long-term prophylaxis (attenuated androgens or C1 esterase inhibitors).[69] Long-term prophylaxis should be individualised to meet patient needs.[69] Overall, allergy and immunology specialists should be involved in the management of angiooedema, and appropriate testing should be offered to family members.[67]

8 | PAP OF GENETIC ORIGIN

A genetic origin for abdominal pain is not frequent but should be considered in case of familial history of similar symptoms or when the patient's origin is from an area of high prevalence, such as the Mediterranean Basin

8.1 | Acute hepatic porphyrias

Acute hepatic porphyrias (AHPs) are a rare and potentially life-threatening subgroup of hereditary porphyrias characterised by neurovisceral attacks with or without cutaneous manifestations.[45,46] AHPs are transmitted in an autosomal dominant manner,[48] and the most frequent porphyria linked to neurovisceral symptoms is acute intermittent porphyria (AIP). The prevalence of AIP in Western populations is approximately one in 1700 individuals, but the penetrance of the gene is low.[46] Most patients are female (90%), and age of onset ranges from 18 to 45 years.[45]

Neurovisceral attacks typically present as severe, diffuse abdominal pain (up to 95% of cases) that increases over several days or recurs over several weeks and is usually accompanied by nausea, vomiting, abdominal distention and guarding, diarrhoea or constipation.[45,47,48] Hyponatraemia, hypochloraemia and hypomagnesaemia may develop. Neurological symptoms can range from subtle signs of fatigue to altered mental status and, in severe cases, seizures and stupor.[45,47,48] Typically, AIP presents in healthy women who report several days of fatigue or mental fogginess with recurrent severe abdominal pain and more severe neurological symptoms.[48,85] As a result, diagnostic orientation is often erratic and delayed by 10 years or more.[48] Many patients with AIP are misdiagnosed and undergo unjustified surgical procedures such as appendectomies, cholecystectomies and hysterectomies.[86] The central diagnostic clue is the identification of acute or recurrent attack triggers, which commonly include porphyrinogenic medications, alcohol, smoking, low-calorie diets, stress and hormonal changes.[45,47] A recent prospective study in AHP patients, mainly AIP, demonstrated that patients reported abdominal pain (92%) and nausea (85%) during attacks, but 65% of patients also reported chronic symptoms between attacks, mainly pain, nausea, tiredness and anxiety.[87]

AHPs arise from a deficiency in one of the enzymes in the haeme biosynthesis pathway, resulting in hepatic accumulation and increased excretion of neurotoxic porphyrins and porphyrin precursors: delta-aminolevulinic acid (ALA) and porphobilinogen (PBG).[45,48]

Diagnosis of AHP is based on elevated concentrations of ALA and PBG in urine and plasma.[45,48] These tests take days to complete and contribute to diagnostic delay, misdirected medical care and poor outcomes. Samples require shielding from light, so consultation with a local porphyrin laboratory on optimal testing is advised for those unfamiliar with testing procedures.[88]

Lead poisoning is a differential diagnosis because its pathophysiological and symptomatic profiles are very similar to those of AHPs (Table 1).[50,51] Chronic lead intoxication blocks glutathione synthesis in addition to several enzymes involved in haeme synthesis, leading to the accumulation of neurotoxic porphyric derivatives.[11,50] Clinical presentation involves impairment of the nervous, haematological and renal systems, with gastrointestinal symptoms (abdominal pain, anorexia, vomiting and constipation) appearing with longer exposures.[50,51] Diagnosis is determined by lead concentrations in blood. Historically caused by lead paint, which has been prohibited in many countries for years, it can occur after drinking water contaminated by corroded lead pipes.[89] Patients generally receive chelation therapy and symptomatic treatment as needed.

While patients mostly remain symptomatic, an acute attack of AHP generally warrants urgent treatment with intravenous human hemin.[45,46] Givosiran, a small interfering RNA, was recently approved for the treatment of AHP.[90–94] In a phase 3 trial, givosiran reduced the mean annualised rate of porphyria attacks over 6 months by 74% versus placebo.[49]

8.2 | Ehlers–Danlos syndrome

Ehlers–Danlos syndrome (EDS) is a heterogeneous group of inherited connective tissue disorders characterised by generalised joint hypermobility, skin hyperextensibility and tissue fragility.[54,95–97] Estimated prevalence is one in 5000.[95] Caused by mutations in collagen-encoding genes or genes encoding collagen-modifying enzymes,[54] many types have been identified. The most common forms are the classical type, hypermobility type and vascular type, which are inherited in an autosomal dominant fashion.[54,96,97] Gastrointestinal symptoms occur in approximately 60% of patients with classical or hypermobile EDS and 50% of those with vascular EDS.[95]

The hypermobile EDS subtype (hEDS) is autosomal dominant but without any clear genetic mutation.[97,98] The clinical diagnosis of hEDS requires (1) generalised joint hypermobility, (2) at least two features of either systemic manifestations of a more generalised connective tissue disorder, positive family history involving at least one first-degree relative or musculoskeletal complication and (3) absence of unusual skin fragility, exclusion of other heritable and acquired connective tissue disorders and exclusion of alternative diagnoses.[99] In a subset of patients, hEDS is linked to a deficiency in tenascin-X, an extracellular glycoprotein matrix that regulates collagen deposition. Associated with a high rate of various functional gastrointestinal disorders, patients with hEDS have significantly more chronic pain, somatic sensitivity and anxiety, along with poorer quality of life compared with patients with other functional gastrointestinal disorders.[95,96,98,100] In a French cohort study, IBS, functional constipation and gastroesophageal reflux disease were reported in 48%, 36% and 79%, respectively, of EDS patients (81% had hEDS).[96] In a separate case–control study, 40% of patients with functional gastrointestinal disorders met criteria for hEDS.[98] A large case–control study addressed the prevalence and associations for functional gastrointestinal disorders in patients with hEDS or hypermobility spectrum disorder (HSD) against age- and sex-matched general population-based controls.[101] Almost all patients with hEDS/HSD (98%, $n = 591/603$) fulfilled symptom-based criteria for Rome IV compared with the population controls (47%, $n = 285/603$).[101] Patients with hEDS/HSD were also significantly more likely to experience abdominal pain at least 1 day per week over the previous 3 months compared with the population controls (75% vs 14%, $p < 0.0001$).[101] Visceroptosis, which is the downward displacement of abdominal organs below their natural positions, has also been reported in patients with hEDS. Visceroptosis can cause kinking of blood vessels and nerves, resulting in severe symptoms.[53,102] Diagnosis is based on clinical symptoms and a positive family history.[54]

Vascular Ehlers–Danlos syndrome (vEDS) affects an estimated one in 150,000 individuals, is more common in men and is believed to result from heterozygous mutations in the *COL3A1* gene, encoding type III collagen.[52] Because collagen occurs in most connective soft tissues, spontaneous bowel perforation and intra-abdominal arterial rupture are common complications. Among 133 patients with vEDS, 41% experienced a wide variety of gastrointestinal manifestations,

with spontaneous colonic perforations or spleen ruptures, and 53% of patients had recurrent events.

Without any specific evidence-based guidelines for the management of gastrointestinal symptoms in EDS, treatment is supportive in nature and largely focused on alleviation of symptoms with proton-pump inhibitors and antihistamines.[53,95] Appropriate precautions should be taken during surgery and endoscopy in patients with vEDS.[53]

8.3 | Low phospholipid-associated cholelithiasis syndrome

Low phospholipid-associated cholelithiasis (LPAC) syndrome is associated with mutation of the *ABCB4* gene that codes for the multidrug resistance 3 (MDR3) protein.[55] Dysfunction of MDR3 reduces biliary phosphatidylcholine concentration, leading to less solubilised cholesterol and precipitation of cholesterol gallstones in the bile ducts. LPAC syndrome occurs in approximately 1% of symptomatic cholelithiasis patients, but it affects about three times more women than men and may account for up to 25% of cases of cholelithiasis in women younger than 30 years. In contrast to classical gallstones, LPAC syndrome occurs primarily in young adulthood and in patients with low or normal body weight. Typical biliary pain is present in over 90% of LPAC syndrome cases.[55] Serious complications include pancreatitis, acute cholangitis and intrahepatic lithiasis, which are more frequently observed in men. Diagnosis requires the presence of two of the following three criteria: (1) age at onset younger than 40 years, (2) recurrence of symptoms after cholecystectomy and (3) presence of hyperechogenic intrahepatic foci on ultrasound.

Medical treatment of LPAC syndrome relies on ursodeoxycholic acid, a hydrophilic biliary acid that has multiple mechanisms to potentiate MDR3 and solubilise cholesterol.[55] Ursodeoxycholic acid provides rapid relief of symptoms. For patients with hypercholesterolaemia, treatment with statins is preferred over fibrates.

8.4 | Familial Mediterranean fever

Familial Mediterranean fever (FMF) is the most common monogenic auto-inflammatory disease described in eastern Mediterranean people,[56] affecting one in 200 to one in 1000 persons in this population.[58] Characterised by recurrent flares of fever associated with polyserositis,[56] patients also experience intense and diffuse abdominal pain often lasting several days. Clinical examinations reveal a tender and tympanic abdomen. Symptoms are sometimes suggestive of a partial occlusion or even ascites, which leads to unnecessary laparotomies.[11,56] On biological examination, C-reactive protein and other inflammatory markers are markedly increased during crisis and rapidly returned to normal value at the end of crisis.[103] Secondary amyloidosis is the major long-term serious complication of FMF.

FMF is caused by mutations in the *MEFV* gene, which encodes pyrin, an element of the NLRP3 inflammasome complex.[56] Among 300 identified sequence variants of *MEFV*, the most common pathogenic variants are M694V, V726A, M680I and M694I; E148Q is the most frequent variant among carriers. FMF is inherited in an autosomal recessive manner.[57] Mutations in the *MEFV* gene are associated with increased IL-1β production, which causes excess inflammation.[56] Diagnosis of FMF relies mainly on clinical findings, and molecular analysis of the *MEFV* gene provides genetic confirmation. Only the most frequent mutations are tested during standard genetic testing, meaning that a negative test does not exclude a diagnosis of FMF. In this case, if the clinical history strongly suggests FMF, a positive therapeutic response to colchicine might be necessary to retain a diagnosis.[56]

Colchicine prophylaxis constitutes the mainstay of FMF management by preventing acute attacks and amyloidosis through reduction of chronic inflammation.[56] IL-1 inhibitors, such as anakinra and rilonacept, are beneficial treatment options for colchicine-resistant or colchicine-intolerant patients.

9 | DYSAUTONOMIA AND CENTRALLY MEDIATED DISORDERS OF PAP

9.1 | Postural orthostatic tachycardia syndrome

Patients diagnosed with POTS have symptoms of orthostatic intolerance for at least 6 months and increases in heart rate of ≥30 bpm within 10 min of standing in the absence of orthostatic hypotension (blood pressure decreases of >20/10 mm Hg).[104] POTS is a common cause of chronic orthostatic intolerance, including the severe orthostatic symptoms of tachycardia, light-headedness, blurred vision, tremor and non-orthostatic symptoms. Urinary and gastrointestinal symptoms (e.g., chronic abdominal pain, bloating, constipation, dyspeptic symptoms) may considerably diminish quality of life.[59] POTS is estimated to affect between 500,000 and 3 million people in the United States,[60] principally women aged between 15 and 50 years.[59] Abdominal pain has been noted in 70%–80% of patients

POTS is a heterogeneous disorder that may have multiple aetiologies.[59,60] The underlying pathophysiology of gastrointestinal symptoms includes dysautonomia, visceral hypersensitivity, central sensitisation, somatic hypervigilance and behavioural amplification.[59] Testing is performed based upon gastrointestinal symptoms and may include endoscopic, radiographic and motility tests. Gastrointestinal symptoms are managed by treating the most prominent symptoms with agents including antiemetics, carbidopa, pyridostigmine, tricyclic antidepressants or other combinations of gut-directed and central agents.

9.2 | Association between MCAS, hEDS and POTS

Largely discussed, substantial overlap in symptoms and/or comorbidities exists between MCAS, hEDS and POTS.[60] However, while POTS is common and has established diagnostic criteria, diagnostic

criteria for MCAS and hEDS are vague. A recent review of the literature concluded that there is a lack of research on any association between the entities, and more stringent diagnostic criteria are needed to minimise false positives.[60]

9.3 | Narcotic bowel syndrome

Narcotic bowel syndrome is characterised by worsening gastrointestinal symptoms in cases of escalating or continuous opioid therapy (Figure 1).[12,61] It is described as chronic, severe to very severe abdominal pain that occurs daily for more than 3 months.[62] Additional gastrointestinal symptoms, such as bloating, constipation, nausea and vomiting, may also be present. Estimates suggest that approximately 5% of patients who take regular opioids develop narcotic bowel syndrome,[12,61] but prevalence is probably underestimated given the current epidemic of opioid abuse.

Opioid-induced, centrally mediated, visceral hyperalgesia probably plays a central role in the aetiology of narcotic bowel syndrome,[61] with potential mechanisms including activation of bimodal opioid regulatory systems, counter-regulatory mechanisms, neuroinflammation, opioid facilitation and interactions of the *N*-methyl D-aspartate receptor with opioids at the level of the spinal cord. Management combines patient education (about the paradoxical worsening mechanism) and an opioid detoxification programme, involving tapering or substitution of opioids, concomitant administration of antidepressants or anxiolytics and implementation of psychological interventions. The success of opioid detoxification regimens depends on several factors such as those associated with failure, including history of substance misuse, concomitant personality disorder, a high current opioid misuse measures score and negativity or failure to engage in discussion of detoxification.[61,105] Due to these factors, recidivism rates remain high in the first year following detoxification.

9.4 | Centrally mediated abdominal pain syndrome (formerly functional abdominal pain syndrome)

Centrally mediated abdominal pain syndrome (CAPS) is a functional disorder impairing daily functioning, characterised by chronic or frequently recurring severe abdominal pain, with little or no relationship to events such as eating, defecation or changes in bowel habits.[12] Patients with PAP should be screened for psychiatric symptoms, illness-related disability and response to stress, which can impact the ability to cope with symptoms. The prevalence of functional abdominal pain has been reported to range from 0.5% to 1.7%, but this may be overestimated because not all criteria, such as impaired daily functioning, were considered.[12]

In patients with CAPS, dysregulation of the brain–gut interaction results in central sensitisation with disinhibition of pain signals rather than increased peripheral afferent excitability.[3,63] Notably, CAPS is not associated with visceral hypersensitivity or altered intestinal motility. In a retrospective review of electronic health records from 103 PAP patients, CAPS was identified in 52 (50%) patients. Of these 52 patients, 58% reported bloating and 50% experienced concomitant nausea and vomiting.[16] A majority of these patients reported other gastrointestinal disease (65%), other functional diagnosis (85%) and a referral to psychology (55%). These findings are indicative of the frustration and abandonment felt by patients with functional abdominal pain.

CAPS is classified and diagnosed using Rome IV criteria.[3] Biological and radiological tests are normal, and patients who are unsatisfied with their treatment seek care from multiple providers, with limited success.[12] Physicians caring for these patients also feel frustrated because of lack of specific diagnostic tests and/or patient dissatisfaction. While there are defined criteria for CAPS and other functional gastrointestinal disorders, these disorders cannot be distinguished structurally or metabolically by currently available diagnostic methods.[13] The pathophysiology of CAPS and other functional gastrointestinal disorders, such as IBS, is likely similar as well, leading to overlap in comorbidities with other pain syndromes, predisposing life events and treatment responses.[13,106] Thus, management of centrally mediated disorders is a complex process that generally requires a multidisciplinary approach.[12]

10 | CONCLUSION

PAP is a challenging condition to diagnose and treat. Many patients undergo repeated diagnostic testing and treatment, including surgery, without achieving symptom relief. Increasing physician awareness of the various causes of PAP, especially of rare diseases that are less well known, may prompt earlier diagnosis and treatment, which may improve patient outcomes. Some causes of PAP can be effectively treated using established approaches after a definitive diagnosis has been reached. Other causes are more complex and may benefit from a multidisciplinary approach involving gastroenterologists, pain specialists, allergists, immunologists, rheumatologists, psychologists, physiotherapists, dieticians and primary care clinicians.

AUTHOR CONTRIBUTIONS

Benoit Coffin conceived the idea to develop the manuscript. **Benoit Coffin** and **Henri Duboc** contributed equally to the drafting and critical review and revisions of all drafts of the manuscript and approved the final version.

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REFERENCES

1. Tolba R, Shroll J, Kanu A, Rizk MK. The epidemiology of chronic abdominal pain. In: Kapural L, editor. Chronic abdominal pain. New York, NY: Springer; 2015. p. 13–24.
2. Lakhoo K, Almario CV, Khalil C, Spiegel BMR. Prevalence and characteristics of abdominal pain in the United States. Clin Gastroenterol Hepatol. 2021;19(9):1864–72.
3. Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical features and Rome IV. Gastroenterology. 2016;150(6):1262–79.
4. van Dulmen AM, Fennis JF, Mokkink HG, van der Velden HG, Bleijenberg G. Doctors' perception of patients' cognitions and complaints in irritable bowel syndrome at an out-patient clinic. J Psychosom Res. 1994;38(6):581–90.
5. Van Dulmen AM, Fennis JF, Mokkink HG, Van der Velden HG, Bleijenberg G. Doctor-dependent changes in complaint-related cognitions and anxiety during medical consultations in functional abdominal complaints. Psychol Med. 1995;25(5):1011–8.
6. Enck P, Aziz Q, Barbara G, Farmer AD, Fukudo S, Mayer EA, et al. Irritable bowel syndrome. Nat Rev Dis Primers. 2016;2:16014.
7. Enck P, Azpiroz F, Boeckxstaens G, Elsenbruch S, Feinle-Bisset C, Holtmann G, et al. Functional dyspepsia. Nat Rev Dis Primers. 2017;3:17081.
8. Thompson WG, Heaton KW, Smyth GT, Smyth C. Irritable bowel syndrome in general practice: prevalence, characteristics, and referral. Gut. 2000;46(1):78–82.
9. Bhatt A, Stevens T. Establishing diagnosis of chronic abdominal pain: gastroenterologist view. In: Kapural L, editor. Chronic abdominal pain. New York, NY: Springer; 2015. p. 25–32.
10. Veizi IE, Wynne M, Hayek SM. Establishing diagnosis of chronic abdominal pain: pain medicine view. In: Kapural L, editor. Chronic abdominal pain. New York, NY: Springer; 2015. p. 33–43.
11. Coffin B, Sabate JM, Jouet P. Persistent abdominal pain. Gastroenterol Clin Biol. 2006;30(3):392–8.
12. Bharucha AE, Chakraborty S, Sletten CD. Common functional gastroenterological disorders associated with abdominal pain. Mayo Clin Proc. 2016;91(8):1118–32.
13. Keefer L, Drossman DA, Guthrie E, Simrén M, Tillisch K, Olden K, et al. Centrally mediated disorders of gastrointestinal pain. Gastroenterology. 2016;150(6):1408–19.
14. Hammer J, Eslick GD, Howell SC, Altiparmak E, Talley NJ. Diagnostic yield of alarm features in irritable bowel syndrome and functional dyspepsia. Gut. 2004;53(5):666–72.
15. Pourmand H, Esmaillzadeh A. Consumption of a low fermentable oligo-, di-, mono-saccharides, and polyols diet and irritable bowel syndrome: a systematic review. Int J Prev Med. 2017;8:104.
16. Kilgallon E, Vasant DH, Green D, Shields PL, Hamdy S, Lal S, et al. Chronic continuous abdominal pain: evaluation of diagnostic features, iatrogenesis and drug treatments in a cohort of 103 patients. Aliment Pharmacol Ther. 2019;49(10):1282–92.
17. Eriksson EM, Andren KI, Kurlberg GK, Eriksson HT. Aspects of the non-pharmacological treatment of irritable bowel syndrome. World J Gastroenterol. 2015;21(40):11439–49.
18. Longstreth GF, Yao JF. Irritable bowel syndrome and surgery: a multivariable analysis. Gastroenterology. 2004;126(7):1665–73.
19. Ringel-Kulka T, Ringel Y. Evaluation of chronic abdominal pain. BMJ Best Pract. 2021;1–41.
20. Sunkara T, Rawla P, Yarlagadda KS, Gaduputi V. Eosinophilic gastroenteritis: diagnosis and clinical perspectives. Clin Exp Gastroenterol. 2019;12:239–53.
21. Hussein MR, Abdelwahed SR. Mesenteric panniculitis: an update. Expert Rev Gastroenterol Hepatol. 2015;9(1):67–78.
22. Barret M, Martineau C, Rahmi G, Pellerin O, Sapoval M, Alsac JM, et al. Chronic mesenteric ischemia: a rare cause of chronic abdominal pain. Am J Med. 2015;128(12):1363.e1361–8.
23. Patel R, Waheed A, Costanza M. Chronic mesenteric ischemia. Treasure Island, FL: StatPearls Publishing; 2021.
24. Terlouw LG, Moelker A, Abrahamsen J, Acosta S, Bakker OJ, Baumgartner I, et al. European guidelines on chronic mesenteric ischaemia—joint united European gastroenterology, European Association for Gastroenterology, endoscopy and nutrition, European Society of Gastrointestinal and Abdominal Radiology, Netherlands Association of Hepatogastroenterologists, Hellenic Society of Gastroenterology, cardiovascular and interventional radiological Society of Europe, and Dutch mesenteric ischemia study group clinical guidelines on the diagnosis and treatment of patients with chronic mesenteric ischaemia. United European Gastroenterol J. 2020;8(4):371–95.
25. van Dijk LJ, van Noord D, de Vries AC, et al. Clinical management of chronic mesenteric ischemia. United European Gastroenterol J. 2019;7(2):179–88.
26. Goodall R, Langridge B, Onida S, Ellis M, Lane T, Davies AH. Median arcuate ligament syndrome. J Vasc Surg. 2020;71(6):2170–6.
27. Gerner-Rasmussen J, Burcharth J, Gogenur I. The efficacy of adhesiolysis on chronic abdominal pain: a systematic review. Langenbecks Arch Surg. 2015;400(5):567–76.
28. Paajanen P, Fagerstrom A, Paajanen H. Laparoscopic adhesiolysis in chronic abdominal pain: 15-year follow-up study. J Clin Gastroenterol. 2018;52(4):e32–6.
29. Molegraaf MJ, Torensma B, Lange CP, Lange JF, Jeekel J, Swank DJ. Twelve-year outcomes of laparoscopic adhesiolysis in patients with chronic abdominal pain: a randomized clinical trial. Surgery. 2017;161(2):415–21.
30. Cotton PB, Elta GH, Carter CR, Pasricha PJ, Corazziari ES. Gallbladder and sphincter of Oddi disorders. Gastroenterology 2016;150:1420–9
31. Bistritz L, Bain VG. Sphincter of Oddi dysfunction: managing the patient with chronic biliary pain. World J Gastroenterol. 2006;12(24):3793–802.
32. Sweetser S. Abdominal wall pain: a common clinical problem. Mayo Clin Proc. 2019;94(2):347–55.
33. Shian B, Larson ST. Abdominal wall pain: clinical evaluation, differential diagnosis, and treatment. Am Fam Physician. 2018;98(7):429–36.
34. Koop H, Koprdova S, Schurmann C. Chronic abdominal wall pain. Dtsch Arztebl Int. 2016;113(4):51–7.
35. Kamboj AK, Hoversten P, Oxentenko AS. Chronic abdominal wall pain: a common yet overlooked etiology of chronic abdominal pain. Mayo Clin Proc. 2019;94(1):139–44.
36. Husebye ES, Pearce SH, Krone NP, Kämpe O. Adrenal insufficiency. Lancet. 2021;397(10274):613–29.
37. Charmandari E, Nicolaides NC, Chrousos GP. Adrenal insufficiency. Lancet. 2014;383(9935):2152–67.
38. Afrin LB, Ackerley MB, Bluestein LS, Brewer JH, Brook JB, Buchanan AD, et al. Diagnosis of mast cell activation syndrome: a global "consensus-2". Diagnosis (Berlin, Germany). 2021;8(2):137–52.
39. Weinstock LB, Pace LA, Rezaie A, Afrin LB, Molderings GJ. Mast cell activation syndrome: a primer for the gastroenterologist. Dig Dis Sci. 2021;66(4):965–82.
40. Valent P, Akin C, Nedoszytko B, Bonadonna P, Hartmann K, Niedoszytko M, et al. Diagnosis, classification and management of mast cell activation syndromes (MCAS) in the era of personalized medicine. Int J Mol Sci. 2020;21(23):9030.

41. Valent P, Akin C, Bonadonna P, Hartmann K, Brockow K, Niedoszytko M, et al. Proposed diagnostic algorithm for patients with suspected mast cell activation syndrome. J Allergy Clin Immunol Pract. 2019;7(4):1125–1133.e1121.
42. Ramsay DB, Stephen S, Borum M, Voltaggio L, Doman DB. Mast cells in gastrointestinal disease. Gastroenterol Hepatol. 2010;6(12):772–7.
43. Valent P, Akin C, Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. Blood. 2017;129(11):1420–7.
44. Systemic mastocytosis. 2019. https://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_id=887&Disease_Disease_Search_diseaseGroup=systemic-mastocytosis&%E2%80%A6. Accessed January 18, 2022
45. Bissell DM, Anderson KE, Bonkovsky HL. Porphyria. N Engl J Med. 2017;377(9):862–72.
46. Sardh E, Harper P, Balwani M, Stein P, Rees D, Bissell DM, et al. Phase 1 trial of an RNA interference therapy for acute intermittent porphyria. N Engl J Med. 2019;380(6):549–58.
47. Tatari MM, McCain JD, Cowdell JC. 28-year-old woman with severe generalized abdominal pain. Mayo Clin Proc. 2019;94(7):1334–8.
48. Guerrero RB, Kloke KM, Salazar D. Inborn errors of metabolism and the gastrointestinal tract. Gastroenterol Clin North Am. 2019;48(2):183–98.
49. Balwani M, Sardh E, Ventura P, Peiró PA, Rees DC, Stölzel U, et al. Phase 3 trial of RNAi therapeutic givosiran for acute intermittent porphyria. N Engl J Med. 2020;382(24):2289–301.
50. Wani AL, Ara A, Usmani JA. Lead toxicity: a review. Interdiscip Toxicol. 2015;8(2):55–64.
51. Marginean CO, Melit LE, Moldovan H, Lupu VV, Marginean MO. Lead poisoning in a 16-year-old girl: a case report and a review of the literature (CARE compliant). Medicine. 2016;95(38):e4916.
52. Frank M, Adham S, Zinzindohoue F, Jeunemaitre X. Natural history of gastrointestinal manifestations in vascular Ehlers-Danlos syndrome: a 17-year retrospective review. J Gastroenterol Hepatol. 2019;34(5):857–63.
53. Fikree A, Chelimsky G, Collins H, Kovacic K, Aziz Q. Gastrointestinal involvement in the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet. 2017;175(1):181–7.
54. Botrus G, Baker O, Borrego E, Ngamdu KS, Teleb M, Gonzales Martinez JL, et al. Spectrum of gastrointestinal manifestations in joint hypermobility syndromes. Am J Med Sci. 2018;355(6):573–80.
55. Goubault P, Brunel T, Rode A, Bancel B, Mohkam K, Mabrut JY. Low-phospholipid associated cholelithiasis (LPAC) syndrome: a synthetic review. J Visc Surg. 2019;156(4):319–28.
56. Sonmez HE, Batu ED, Ozen S. Familial Mediterranean fever: current perspectives. J Inflamm Res. 2016;9:13–20.
57. Ozen S, Batu ED, Demir S. Familial Mediterranean fever: recent developments in pathogenesis and new recommendations for management. Front Immunol. 2017;8:253.
58. Familial Mediterranean Fever Statistics. 2020. https://ghr.nlm.nih.gov/condition/familial-mediterranean-fever#statistics. Accessed January 18, 2022.
59. DiBaise JK, Harris LA, Goodman B. Postural tachycardia syndrome (POTS) and the GI tract: a primer for the gastroenterologist. Am J Gastroenterol. 2018;113(10):1458–67.
60. Kohn A, Chang C. The relationship between hypermobile Ehlers-Danlos syndrome (hEDS), postural orthostatic tachycardia syndrome (POTS), and mast cell activation syndrome (MCAS). Clin Rev Allergy Immunol. 2020;58(3):273–97.
61. Farmer AD, Gallagher J, Bruckner-Holt C, Aziz Q. Narcotic bowel syndrome. Lancet Gastroenterol Hepatol. 2017;2(5):361–8.
62. Azizi Z, Javid Anbardan S, Ebrahimi DN. A review of the clinical manifestations, pathophysiology and management of opioid bowel dysfunction and narcotic bowel syndrome. Middle East J Dig Dis. 2014;6(1):5–12.
63. Schmulson MJ, Drossman DA. What is new in Rome IV. J Neurogastroenterol Motil. 2017;23(2):151–63.
64. Maddern J, Grundy L, Castro J, Brierley SM. Pain in endometriosis. Front Cell Neurosci. 2020;14:590823.
65. Ek M, Roth B, Ekström P, Valentin L, Bengtsson M, Ohlsson B. Gastrointestinal symptoms among endometriosis patients—a case-cohort study. BMC Womens Health. 2015;15:59.
66. Gruber TM, Mechsner S. Pathogenesis of endometriosis: the origin of pain and subfertility. Cell. 2021;10(6):1381.
67. Nzeako UC. Diagnosis and management of angioedema with abdominal involvement: a gastroenterology perspective. World J Gastroenterol. 2010;16(39):4913–21.
68. Bork K, Staubach P, Eckardt AJ, Hardt J. Symptoms, course, and complications of abdominal attacks in hereditary angioedema due to C1 inhibitor deficiency. Am J Gastroenterol. 2006;101(3):619–27.
69. Gower RG, Busse PJ, Aygören-Pürsün E, Barakat AJ, Caballero T, Davis-Lorton M, et al. Hereditary angioedema caused by c1-esterase inhibitor deficiency: a literature-based analysis and clinical commentary on prophylaxis treatment strategies. World Allergy Organ J. 2011;4(2 suppl):S9–S21.
70. Srinivasan R, Greenbaum DS. Chronic abdominal wall pain: a frequently overlooked problem. Practical approach to diagnosis and management. Am J Gastroenterol. 2002;97(4):824–30.
71. Swank DJ, Swank-Bordewijk SC, Hop WC, van Erp W, Janssen IMC, Bonjer HJ, et al. Laparoscopic adhesiolysis in patients with chronic abdominal pain: a blinded randomised controlled multi-Centre trial. Lancet. 2003;361(9365):1247–51.
72. McGarrity TJ, Peters DJ, Thompson C, McGarrity SJ. Outcome of patients with chronic abdominal pain referred to chronic pain clinic. Am J Gastroenterol. 2000;95(7):1812–6.
73. Costanza CD, Longstreth GF, Liu AL. Chronic abdominal wall pain: clinical features, health care costs, and long-term outcome. Clin Gastroenterol Hepatol. 2004;2(5):395–9.
74. Lindsetmo RO, Stulberg J. Chronic abdominal wall pain—a diagnostic challenge for the surgeon. Am J Surg. 2009;198(1):129–34.
75. van Assen T, Boelens OB, Kamphuis JT, Scheltinga MR, Roumen RM. Construction and validation of a questionnaire distinguishing a chronic abdominal wall pain syndrome from irritable bowel syndrome. Frontline Gastroenterol. 2012;3(4):288–94.
76. Sellman MS, Mayer RF. Thoracoabdominal radiculopathy. South Med J. 1988;81(2):199–201.
77. Quénéhervé L, Drui D, Blin J, Péré M, Coron E, Barbara G, et al. Digestive symptoms in daily life of chronic adrenal insufficiency patients are similar to irritable bowel syndrome symptoms. Sci Rep. 2021;11(1):8077.
78. Desramé J, Sabaté JM, Agher R, Bremont C, Gaudric M, Couturier D, et al. Assessment of hypothalamic-pituitary-adrenal axis function after corticosteroid therapy in inflammatory bowel disease. Am J Gastroenterol. 2002;97(7):1785–91.
79. Wilder-Smith CH, Drewes AM, Materna A, Olesen SS. Symptoms of mast cell activation syndrome in functional gastrointestinal disorders. Scand J Gastroenterol. 2019;54(11):1322–5.
80. Jennings S, Russell N, Jennings B, Slee V, Sterling L, Castells M, et al. The Mastocytosis Society survey on mast cell disorders: patient experiences and perceptions. J Allergy Clin Immunol Pract. 2014;2(1):70–6.
81. Akin C. Mast cell activation syndromes. J Allergy Clin Immunol. 2017;140(2):349–55.
82. Giannetti A, Filice E, Caffarelli C, Ricci G, Pession A. Mast cell activation disorders. Medicina. 2021;57:124.
83. Frieri M. Mast cell activation syndrome. Clin Rev Allergy Immunol. 2018;54(3):353–65.

84. Weinstock LB, Brook JB, Walters AS, Goris A, Afrin LB, Molderings GJ. Mast cell activation symptoms are prevalent in long-COVID. Int J Infect Dis. 2021;112:217–26.
85. Ratner M. Patients with porphyria bask in sunlight of FDA approval. Nat Biotechnol. 2019;37(12):1390–1.
86. Bonkovsky HL, Maddukuri VC, Yazici C, Anderson KE, Bissell DM, Bloomer JR, et al. Acute porphyrias in the USA: features of 108 subjects from porphyrias consortium. Am J Med. 2014;127(12):1233–41.
87. Gouya L, Ventura P, Balwani M, Bissell DM, Rees DC, Stölzel U, et al. EXPLORE: a prospective, multinational, natural history study of patients with acute hepatic porphyria with recurrent attacks. Hepatology. 2020;71(5):1546–58.
88. Woolf J, Marsden JT, Degg T, Whatley S, Reed P, Brazil N, et al. Best practice guidelines on first-line laboratory testing for porphyria. Ann Clin Biochem. 2017;54(2):188–98.
89. Ruckart PZ, Ettinger AS, Hanna-Attisha M, Jones N, Davis SI, Breysse PN. The Flint water crisis: a coordinated public health emergency response and recovery initiative. J Public Health Manag Pract. 2019;25(suppl 1, Lead Poisoning Prevention):S84-S90.
90. Alnylam announces approval of GIVLAARI® (givosiran) in Brazil for the treatment of acute hepatic porphyria (AHP) in adults. [press release] 2020. https://investors.alnylam.com/sites/default/files/GIVLAARI-Brazil-Approval-Press-Release.pdf. Accessed January 18, 2022.
91. Givlaari [package insert]. Cambridge, MA: Alnylam Pharmaceuticals; 2021.
92. Givlaari [summary of product characteristics]. 2021. https://www.ema.europa.eu/en/documents/product-information/givlaari-epar-product-information_en.pdf. Accessed January 18, 2022.
93. Givlaari Canada [product monograph]. Amsterdam, Netherlands: Alnylam Netherlands; 2020.
94. Obtained manufacturing and marketing approval for "Giblari" for the treatment of acute hepatic porphyria [press release]. 2021. https://www.alnylam.jp/sites/default/files/news-articles/Japan_Givo_Approval_Press_Release_0.pdf. Accessed January 18, 2022.
95. Nelson AD, Mouchli MA, Valentin N, Deyle D, Pichurin P, Acosta A, et al. Ehlers Danlos syndrome and gastrointestinal manifestations: a 20-year experience at Mayo Clinic. Neurogastroenterol Motil. 2015;27(11):1657–66.
96. Zeitoun JD, Lefevre JH, de Parades V, et al. Functional digestive symptoms and quality of life in patients with Ehlers-Danlos syndromes: results of a national cohort study on 134 patients. PloS ONE. 2013;8(11):e80321.
97. Beighton P, De Paepe A, Steinmann B, Tsipouras P, Wenstrup RJ. Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos support group (UK). Am J Med Genet. 1998;77(1):31–7.
98. Fikree A, Aktar R, Grahame R, Hakim AJ, Morris JK, Knowles CH, et al. Functional gastrointestinal disorders are associated with the joint hypermobility syndrome in secondary care: a case-control study. Neurogastroenterol Motil. 2015;27(4):569–79.
99. Malfait F, Francomano C, Byers P, Belmont J, Berglund B, Black J, et al. The 2017 international classification of the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet. 2017;175(1):8–26.
100. Castori M, Morlino S, Pascolini G, Blundo C, Grammatico P. Gastrointestinal and nutritional issues in joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type. Am J Med Genet C Semin Med Genet. 2015;169c:54–75.
101. Lam CY, Palsson OS, Whitehead WE, Sperber AD, Tornblom H, Simren M, et al. Rome IV functional gastrointestinal disorders and health impairment in subjects with hypermobility spectrum disorders or hypermobile Ehlers-Danlos syndrome. Clin Gastroenterol Hepatol. 2021;19(2):277–287.e273.
102. Reinstein E, Pimentel M, Pariani M, Nemec S, Sokol T, Rimoin DL. Visceroptosis of the bowel in the hypermobility type of Ehlers-Danlos syndrome: presentation of a rare manifestation and review of the literature. Eur J Med Genet. 2012;55(10):548–51.
103. Mercan R, Bitik B, Eren R, Dumludag B, Turan A, Kucuk H, et al. Underlying causes of persistently elevated acute phase reactants in patiens with familial Mediterranean fever [abstract]. Pediatr Rheumatol. 2015;13(1):P139.
104. Raj SR. Postural tachycardia syndrome (POTS). Circulation. 2013;127(23):2336–42.
105. Kurlander JE, Drossman DA. Diagnosis and treatment of narcotic bowel syndrome. Nat Rev Gastroenterol Hepatol. 2014;11(7):410–8.
106. Kim SE, Chang L. Overlap between functional GI disorders and other functional syndromes: what are the underlying mechanisms? Neurogastroenterol Motil. 2012;24(10):895–913.

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