Chronic intestinal pseudo-obstruction

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Literature review current through: Oct 2020. | **This topic last updated:** Oct 29, 2020.

INTRODUCTION

Pseudo-obstruction is a syndrome characterized by signs and symptoms of a mechanical obstruction of the small or large bowel in the absence of an anatomic lesion that obstructs the flow of intestinal contents. Pseudo-obstruction may be acute or chronic and is characterized by the presence of dilation of the bowel on imaging. When there is evidence of chronic small intestinal motility disorder in the absence of bowel dilatation, the preferred term is chronic intestinal dysmotility.

This topic review will discuss the etiology, clinical manifestations, diagnosis, and treatment of chronic intestinal pseudo-obstruction. Acute pseudo-obstruction, chronic intestinal dysmotility, and slow transit constipation/colon inertia are discussed separately. (See "Acute colonic pseudo-obstruction (Ogilvie's syndrome)" and "Etiology and evaluation of chronic constipation in adults".)

ETIOLOGY

Chronic intestinal pseudo-obstruction (CIPO) is a rare disorder that may be due to an underlying neuropathic disorder (involving the enteric nervous system or extrinsic nervous system), a myopathic disorder (involving the smooth muscle), or abnormality

in the interstitial cell of Cajal (ICC) [1]. Therefore, there are parallels in the pathobiological mechanisms of CIPO and gastroparesis.

Neuropathic, myopathic, or ICC abnormalities may be idiopathic or secondary to another disease. Approximately half of the cases of CIPO are secondary to neurologic, paraneoplastic, autoimmune, metabolic/endocrine, and infectious diseases.

More than one of the elements of the neuromuscular apparatus of the gut may be affected in certain diseases. For example, there is an intrinsic neuropathic phase of scleroderma, before the smooth muscle involvement results in myopathy. Similarly, mitochondrial cytopathy first results in neuropathy and eventually myopathy. Moreover, diabetes affects extrinsic nerves through autonomic neuropathy, and the ICCs and amyloidosis causes an extrinsic neuropathy followed by myopathic CIPO. A case series that evaluated 14 parameters in full thickness small intestinal biopsies from 19 patients with CIPO or chronic enteric dysmotility showed heterogeneous functional abnormalities, with the most prevalent abnormality being decreased purinergic neuromuscular transmission, which was detected in 44 percent of jejunal samples. This suggests that the neuromuscular impairment cannot be attributed to a single mechanism [2].

Degenerative neuropathies — Neurologic (eg, Parkinson disease and Shy-Drager syndrome) and metabolic disorders (eg, diabetes mellitus) can affect the extrinsic nerve pathways supplying the gut. Degenerative neuropathies may result from several putative pathogenetic mechanisms, including altered calcium signaling, mitochondrial dysfunction, and production of free radicals, leading to degeneration and loss of gut intrinsic neurons [3]. Neuropathic disorders may be complicated by a myopathic stage when the muscle layer is infiltrated, as in primary or secondary amyloidosis.

Paraneoplastic immune-mediated pseudo-obstruction — CIPO has been reported in association with small cell lung cancers or carcinoid tumors and malignant thymoma [4,5] or prostate cancer [6]. These patients often have antineuronal nuclear (anti-Hu) antibodies [7]. The antibody is postulated to be directed toward an epitope that is shared between the neuronal elements within the enteric nervous system and the underlying malignancy [8]. Paraneoplastic syndromes may evoke an inflammatory/immune infiltrate targeting neurons located in both submucosal and myenteric ganglia of the enteric nervous system (ENS) [9]; the cellular infiltrate along

with circulating antineuronal antibodies is thought to damage the enteric reflexes, thereby contributing to paraneoplastic dysmotility. (See "Overview of paraneoplastic syndromes of the nervous system" and "Paraneoplastic syndromes affecting spinal cord, peripheral nerve, and muscle", section on 'Autonomic neuropathy'.)

Immune-mediated pseudo-obstruction — Immune-mediated pseudo-obstruction associated with neuronal or smooth muscle involvement has been reported [10,11]. Scleroderma, dermatomyositis, and systemic lupus erythematosus can alter the enteric nerves, the smooth muscle cells, and possibly the ICC [12,13].

In one case report, CIPO resulted from the development of antibodies to buserelin, an analogue of gonadotropin-releasing hormone (GNRH), leading to the immune-mediated destruction of myenteric neurons [14]. A small proportion of patients with inflammatory enteric neuropathy have antibodies directed towards neuronal ion channels (voltage-gated potassium channels and neuronal alpha3-AChR) [15].

Infectious — Chagas disease is the most common infectious cause of CIPO. It is endemic to certain countries, such as Brazil, and is infrequently encountered in patients in the United States unless they have lived for extended periods in South America.

Viruses may cause morphologic (ie, inflammatory) or functional changes of the enteric nervous system and extrinsic neural pathways supplying the gut and are detectable in a subset of patients with CIPO.

A potential role of a chronic JC virus (of the Polyoma virus family) infection has been suggested in observational studies [16,17]. In one case-control study comparing specimens from 10 patients with CIPO with 61 control specimens, JC virus proteins (TAg and VP1) were identified in glial cells of the myenteric plexus in 7 out of 10 adult patients with idiopathic CIPO and in none of the control specimens [16]. TAg and VP1 were selectively expressed in the myenteric plexuses, indicating an active lytic infection, which would be expected to destroy the host cell. (See "Overview of JC polyomavirus, BK polyomavirus, and other polyomavirus infections".)

Radiotherapy and chemotherapy — CIPO has been described in association with radiotherapy and chemotherapy for gynecological cancer [18].

Genetic — Although most cases of CIPO are sporadic, rare familial cases have been described suggesting an underlying genetic basis [19]. A very localized form of genetic neuromuscular denervation or aganglionosis, Hirschsprung disease, is associated with secondary dilatation proximal to the affected segment. Other syndromes associated with mitochondrial cytopathy are also associated with CIPO, including mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), and myoclonus epilepsy associated with ragged-red fibers (MERRF) [20]. (See "Congenital aganglionic megacolon (Hirschsprung disease)" and "Mitochondrial myopathies: Clinical features and diagnosis", section on 'MELAS'.)

Genetic mutations have been described in animal models of congenital pseudo-obstruction and in rare human syndromes [21]. One such syndrome associated with CIPO is Waardenburg-Shah syndrome (deafness and pigmentary abnormalities in association with aganglionic megacolon), in which mutations in neural crest-derived cells have been identified in some kindreds [22]. Dominant mutations in the smooth muscle actin gene, *ACTG2*, account for 44 to 50 percent of CIPO patients. Other recessive or X-linked genes, including *MYLK, LMOD1, RAD21, MYH11, MYL9,* and *FLNA* were reported in single cases.

CIPO has been described in association with the following genetic abnormalities, and these conditions are often associated with congenital abnormalities affecting other organs, including the heart [23-25]:

- Transcription factor SOX10 on chromosome 22 (22p12). De novo *Sox 10* genetic variant (defined as c.895delC) has been associated with CIPO presenting in infancy in association with Waardenburg syndrome type IV, which is characterized by pigmentary abnormalities, and deafness but without Hirschsprung's disease [26].

- *MYH11* genetic mutation [27] – Whole-exome sequencing was used to study 23 independent CIPO families including one extended family with 13 affected members. An autosomal dominantly inherited rare mutation, c.5819delC (p.Pro1940HisfsTer91), in the smooth muscle myosin gene, *MYH11*, was found in the extended family, shared by seven affected family members but not by three unaffected family members with available DNA, suggesting a high probability of genetic linkage. Gene burden analysis indicates that additional genes, *COL4A1*, *FBLN1*, and *HK2*, may be associated with the disease.

- DNA polymerase gamma gene (POLG) on chromosome 21 (21q17).
- Locus on chromosome 8.
- Mutations in filamin A gene (*FLNA*) and L1 cell adhesion molecule (*L1CAM*), which causes X-linked inherited CIPO. Loss-of-function mutations in *FLNA* cause an X-linked dominant disorder with multiple organ involvement. Affected females present with periventricular nodular heterotopia in the brain, cardiovascular complications, thrombocytopenia, and Ehlers-Danlos syndrome [28].
- *ACTG2* (actin, gamma2) disorders result in different phenotypes: megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS), prune-belly syndrome, or CIPO [29]. A novel mutation has been reported in association with visceral myopathy, CIPO, intestinal malrotation, hypertrophic pyloric stenosis, and choledochal cyst [30]. Heterozygous missense variants in ACTG2 were identified in 7 of 17 families (~41 percent) diagnosed with CIPO and its associated conditions from a study of pediatric and adult patients with primary CIPO and suspected visceral myopathy with features of hypoperistalsis syndrome from several centers in Australia and New Zealand [31].

  Using a combination of whole exome and Sanger sequencing, a mutational hotspot in the *ACTG2* gene was identified in almost 50 percent of probands from 111 families with CIPO associated with megacystis. Some cases had affected parents. The importance of this observation is that knowledge of a pathogenic variant in a parent, with a 50 percent risk of recurrence, provides an opportunity for genetic counseling [32].

  Similar phenotypes of visceral myopathy have been reported in association with variants in *ACTG2, ACTA2,* and *MYH11* [33].

  In a study of 53 families [34] with visceral myopathy, using a combination of targeted *ACTG2* sequencing and exome sequencing, analysis of specific residues suggests a severity spectrum of p.Arg178>p.Arg257>p.Arg40 along with other less frequently reported sites p.Arg63 and p.Arg211. These results provide genotype-phenotype correlation for *ACTG2*-related disease and demonstrate the importance of arginine missense changes in visceral myopathy.

- Mutations of the thymidine phosphorylase gene (TP or endothelial cell growth factor-1, ECGF1), which causes familial mitochondrial neurogastrointestinal encephalomyopathy.
- Mutations in *RAD21* that disrupt the ability of its product to regulate genes such as *RUNX1* and *APOB* [35]. *RAD21* is an essential gene that encodes a DNA double-strand break repair protein that is evolutionarily conserved and is essential for proper chromosome segregation, post-replicative DNA repair, and prevention of inappropriate recombination between repetitive regions [36].
- Expression of phosphatase and tensin homolog deleted on chromosome 10 (Pten, a phosphatase critical for controlling cell growth, proliferation, cell death and ENS development), reduced in the giant ganglia of patients with intestinal neuronal dysplasia and from the aganglionic region of Hirschsprung disease.
- Upregulation of the RNA-binding protein for multiple splicing 2 (*RBPMS2*) [37]. This protein is expressed strongly during the early stage of visceral smooth muscle cell (SMC) development and quickly downregulated in differentiated and mature SMCs. Sustained expression of *RBPMS2* inhibits the expression of markers of SMC differentiation by inhibiting bone morphogenetic protein activity, and stimulates SMC proliferation.
- Ehlers-Danlos syndrome due to small bowel α-actin deficiency [38].
- Lysosomal storage disease or Fabry disease (due to X-linked deficiency in lysosomal α-Gal A) may be associated with CIPO [39]; colonic dysmotility has been associated with glycolipid deposition in plexuses and ganglia [39]. These genetic mutations may require investigation of tissue samples by exome sequencing, as was reported for *ACTG2* mutation [40] or systematic histopathological examination of tissue [41]. In fact, disturbances in smooth muscle α-actin expression in intestinal smooth muscle were demonstrated histopathologically in 24 percent of 115 patients with apparently idiopathic CIPO [42].
- Autosomal dominant hereditary intestinal neuropathy linked to a 9.7 Mb region in Chromosome 9 including a 1.2 Mb duplication in a Swedish family with several cases of CIPO [43].

EPIDEMIOLOGY

Chronic intestinal pseudo-obstruction (CIPO) is rare, and most estimates of the incidence and prevalence are from tertiary referral centers. In a national survey in Japan, the estimated prevalence of CIPO was 0.80 to 1.00 per 100,000, with an incidence of 0.21 to 0.24 per 100,000 [44]. The mean age at diagnosis was 63.1 years for males and 59.2 for females.

CLINICAL MANIFESTATIONS

Clinical features — Abdominal pain, bloating, and distension are the most common clinical features of chronic intestinal pseudo-obstruction (CIPO). These symptoms may be acute, recurrent, or chronic.

The most common features at diagnosis in one series of 59 patients included [45,46]:

- Abdominal distension – 75 percent
- Abdominal pain – 58 percent
- Nausea – 49 percent
- Constipation – 48 percent
- Heartburn/regurgitation – 46 percent
- Fullness – 44 percent
- Epigastric pain/burning – 34 percent
- Early satiety – 37 percent
- Vomiting – 36 percent

Acute episodes are characterized by abrupt onset of intense, cramping pain, abdominal distention, nausea, and vomiting. After the acute episode, patients may be asymptomatic or more often, continue to experience symptoms due to delayed transit in the proximal (eg, anorexia, early satiety nausea and vomiting) and/or distal (constipation) gastrointestinal tract. When patients develop these acute exacerbations, it is important to exclude intestinal volvulus [47,48], which may potentially result in vascular compromise.

Patients may have diarrhea due to small bowel bacterial overgrowth. (See "Small intestinal bacterial overgrowth: Clinical manifestations and diagnosis".)

Weight loss results from impaired intestinal transit, malabsorption due to bacterial overgrowth, and inadequate intake due to exacerbation of symptoms with food ingestion.

Patients may have symptoms due to the underlying disorder (eg, dysphagia in CIPO related to Chagas disease, proximal muscle weakness leading to difficulty climbing stairs in patients with polymyositis/dermatomyositis, bladder dysfunction in neuropathic and myopathic CIPO). (See "Manifestations of multiple sclerosis in adults" and "Clinical manifestations and diagnosis of systemic sclerosis (scleroderma) in adults" and "Clinical manifestations of hypothyroidism" and "Clinical manifestations of hypocalcemia" and "Clinical presentation and diagnosis of pheochromocytoma" and "Screening for diabetic polyneuropathy" and "Chronic Chagas cardiomyopathy: Clinical manifestations and diagnosis" and "Congenital aganglionic megacolon (Hirschsprung disease)".)

Patient may provide a history of culprit medications (including anticholinergic antidepressants, calcium channel blockers, and the alpha-2 adrenergic agonists such as clonidine, or cancer immunotherapy with immune checkpoint inhibitors [49]) or a family history of relatives with a similar clinical presentation (eg, mitochondrial neurogastrointestinal encephalopathy [MNGIE], familial amyloidosis) [50].

Physical examination — The main physical findings are abdominal distention, abdominal tenderness on palpation (localized to the epigastric and periumbilical regions or more commonly, over the whole abdomen), and a succussion splash. (See "Gastric outlet obstruction in adults", section on 'Physical examination'.)

Patients may also have signs of an underlying collagen vascular or neuromuscular disease (eg, proximal muscle weakness may indicate polymyositis/dermatomyositis; classic skin abnormalities associated with scleroderma; ptosis, ophthalmoplegia, peripheral polyneuropathy, and sensorineural hearing loss in MNGIE). (See "Clinical manifestations of dermatomyositis and polymyositis in adults" and "Clinical manifestations and diagnosis of systemic sclerosis (scleroderma) in adults" and "Manifestations of multiple sclerosis in adults".)

Laboratory studies — Measurement of serum electrolytes may reveal hypokalemia and metabolic acidosis if there is prominent diarrhea. Hypokalemia and metabolic alkalosis may be present if there is prominent vomiting. Patients may also have

hypoalbuminemia due to malnutrition. Rarely, serum vitamin B12 concentrations are low due to bacterial overgrowth. Patients may have an elevated TSH due to underlying hypothyroidism. Search for auto-antibodies (specific antibodies to glutamic acid decarboxylase, voltage-gated calcium channels [P/Q subtype], nicotinic acetylcholine receptors, and voltage-gated potassium channels) may identify an association of an immune-mediated process [51].

Imaging — A plain film of the abdomen in intestinal pseudo-obstruction usually demonstrates air-fluid levels and/or distended loops of small bowel. In addition, computed tomographic/magnetic resonance enterography may demonstrate dilated loops and rarely diverticula or pneumatosis intestinalis [52].

Radiographic testing does not usually provide an etiologic diagnosis of CIPO. An exception is systemic sclerosis affecting the small intestine, which is characterized by dilated segments, edema, and abnormal texture and motility of the valvulae conniventes (image 1). (See "Gastrointestinal manifestations of systemic sclerosis (scleroderma)".)

DIAGNOSIS

The diagnosis of chronic intestinal pseudo-obstruction (CIPO) is based on the presence of longstanding symptoms of mechanical obstruction in the absence of an anatomic cause on radiologic examination and endoscopy, and evidence of impaired motility.

Confirmation of the diagnosis requires exclusion of mechanical obstruction and other causes of dysmotility by performing imaging studies, endoscopy, and scintigraphy to assess motility.

Imaging — When there is clinical suspicion of CIPO due to symptoms of obstruction, patients should undergo initial evaluation with radiographic testing to exclude organic causes of obstruction. Plain radiographs identify air-fluid levels, and contrast imaging (computed tomographic [CT]/magnetic resonance [MR] enterography) identifies an organic cause of obstruction. MR angiography should be considered in patients with evidence of obstruction when congenital or acquired vascular abnormalities are suspected based on enterography. Cine MR imaging may be used to assess small

bowel motility in patients with CIPO by quantitative analysis of luminal diameter, however, further studies are needed to validate these results [53,54].

Endoscopy — Upper endoscopy and colonoscopy should be performed to rule out an intraluminal or extraluminal cause of obstruction and to identify the location of the obstruction (upper [gastrojejunal] or lower [ileocolonic] gastrointestinal tract). Upper gastrointestinal endoscopy is useful to exclude an aorto-mesenteric artery compression syndrome, which may be difficult to differentiate on imaging from CIPO due to the impact of severe dysmotility on this segment of the small intestine (ie, sustained uncoordinated contractions in the distal duodenum). The duodenal mucosa should be biopsied to exclude celiac disease.

Motility assessment — In patients in whom CIPO is suspected and there is no evidence of an intraluminal or extraluminal cause of obstruction on imaging and by endoscopy, the presence of a motility disorder should be confirmed with scintigraphy.

Scintigraphy — Scintigraphy is the method of choice in the evaluation of gastric, small bowel, and colon transit.

Normal small bowel transit time can vary depending on the methods used. Using resin pellets mixed with a meal, small bowel transit time in healthy individuals reportedly ranged from 151 to 290 minutes [55]. Using the liquid phase of a mixed solid–liquid meal, small bowel transit time ranged from 72 to 392 minutes in healthy individuals [56].

While interpreting scintigraphy results, it is important to note that delayed colonic transit may cause delayed small bowel transit. Therefore, it is important to consider gastrointestinal transit in all three main regions (stomach, small bowel, and colon) before concluding that delayed small bowel transit defines small intestinal dysmotility. A useful clue to clinically significant small intestinal disease is the finding of delayed gastric emptying [57,58]. Thus, when small bowel and colonic transit are delayed and gastric emptying is normal, the main focus of treatment should be normalization of colonic motor function and treatment of constipation, rather than attempting to normalize the small bowel transit alone. Novel approaches using fewer scans have been devised to simplify the evaluation of bowel transit using scintigraphy [55,59,60]. However, there is a wide range of normality (essentially 0 to 100 percent in a sample of 319 healthy volunteers) in the surrogate endpoint of small bowel transit commonly

used in scintigraphic studies that is the percent colonic filling at six hours. Therefore, small bowel transit measurement may require more scans to have sufficient specificity to diagnose intestinal motility disorder and in these situations, careful assessment of gastric and colonic transit is also key.

Wireless motility capsule — Small bowel transit in suspected chronic intestinal dysmotility can also be measured by wireless motility capsule, which assesses small bowel transit time by a sharp increase in pH on entry into the duodenum and by a fall in pH at the ileocecal junction [61]. Evaluation of intestinal motility using endoluminal image analysis acquired by capsule has also been developed [62]. However, further validation of these techniques is needed before they can be routinely used to assess motility. (See "Overview of gastrointestinal motility testing" and "Etiology and evaluation of chronic constipation in adults", section on 'Wireless motility capsule'.)

DIFFERENTIAL DIAGNOSIS

Chronic intestinal dysmotility and slow transit constipation/colon inertia are similar motor disorders of the small bowel and colon, which are not associated with dilatation (table 1). Chronic intestinal pseudo-obstruction can be distinguished from mechanical obstruction and other acute functional causes of obstruction (eg, postoperative ileus and acute pseudo-obstruction) based on the time course, location of dilation, symptom progression, and findings on imaging (table 2). The differentiation of CIPO (encompassing heterogeneous conditions leading to severe, end-stage gut motor failure and defined clinically and radiologically by evidence of abnormal small bowel motility and episodic or chronic signs mimicking mechanical obstruction) from enteric dysmotility (defined as demonstrable abnormal small bowel motor activity but without any features mimicking mechanical obstruction) is relevant since CIPO is more likely to require long-term home parenteral nutrition [63].

IDENTIFYING THE ETIOLOGY

Once the diagnosis of chronic intestinal pseudo-obstruction (CIPO) is established, the underlying etiology should be determined. All patients should undergo laboratory testing to identify secondary causes of CIPO.

In patients with delayed transit on scintigraphy, in whom there is a known underlying disease, no further investigation is necessary (see 'Etiology' above). In patients with delayed transit and no known underlying disease, manometry should be performed. Autonomic testing is useful in patients with evidence of neuropathic dysmotility on manometry, but without a known underlying neurologic disorder. Full thickness biopsy is rarely needed and should be considered in patients with severe dysmotility of unknown etiology who undergo surgery, in patients with poor postsurgical outcomes, or in patients with a permanent catheter for enteral or parenteral nutrition.

Laboratory studies — Laboratory examination can identify secondary causes of CIPO related to potentially curable diseases. The following tests should therefore be performed in all patients with CIPO: complete blood count, electrolytes, liver tests, vitamin B12, folate, celiac serologies, thyrotropin (TSH), serologic testing for herpes simplex virus (HSV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), markers of inflammation including erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP).

Antineuronal antibodies (ANNA-1/anti-Hu) should be sought in patients with suspected paraneoplastic syndrome [64]. In patients with suspected mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) lactic acid (at rest and during exercise), thymidine phosphorylase levels in the buffy coat, nucleotide concentrations, and genetic analysis should be performed.

Manometry — Manometric studies of the esophagus, stomach and small intestine should be performed in patients with abnormal motility on scintigraphy, but no known underlying disease [65,66]. Manometry plays a supportive role in defining the underlying diagnosis, but lacks specificity. Myopathic disorders are typically associated with low amplitude contractions, whereas in neuropathic disorders, the amplitude of contractions is typically normal, but the organization of the contractile response is abnormal (image 2). A mechanical obstruction of the intestine typically shows simultaneous, prolonged contractions at the level of the small intestine [67]. Of note, esophageal manometry may show ineffective peristalsis in about half the patients with CIPO [68].

Technique — Manometry is performed by placement of a multilumen tube through the nose or mouth into the small intestine. Positioning of the tube is facilitated by

endoscopy or a steerable catheter system to place a guidewire through the stomach and duodenum and into the jejunum. Perfusion of the lumens or solid state transducers placed along the tube allows measurement of the pressure profile of the stomach and small intestine. These profiles are measured over several hours during fasting and after standard meals.

Autonomic testing — Autonomic testing is useful in patients with evidence of neuropathic dysmotility on manometry, but without a known underlying neurologic disorder. Several common neurologic disorders can affect gastrointestinal motility by altering the parasympathetic or sympathetic supply to the gut (figure 1). These include [50]:

- Brainstem tumors or strokes
- Diabetes mellitus
- Spinal cord injury
- Multiple sclerosis
- Parkinson disease
- Autonomic system degeneration

Tests of autonomic function can differentiate a preganglionic or central lesion from a peripheral neuropathy associated with autonomic dysfunction (table 3) [69].

Brain and spinal cord magnetic resonance imaging (MRI) is essential in patients in whom a central lesion is suggested from the history or the results of autonomic testing. A peripheral dysautonomia requires further screening for a toxic, metabolic, or paraneoplastic process (eg, lead poisoning, porphyria, or lung cancer, respectively).

Full-thickness intestinal biopsy — Full thickness biopsies should be considered in patients with severe dysmotility of unknown etiology who undergo surgery for any reason especially in those refractory to therapy, in patients with poor postsurgical outcomes, or in patients with a permanent catheter for enteral or parenteral nutrition. Histologic findings may help differentiate myopathic, neuropathic, or other disorders. Histopathologic techniques also allow for detection of subtle abnormalities in the enteric nervous system and underlying deficiencies in specific neuropeptides and neurotransmitters, thereby providing valuable information for diagnosis, prognosis, and management [1,10,70,71]. Case reports have described histologic findings on full-

thickness specimens and/or their correlation to manometric findings [72-74]. (See 'Prognosis' below.)

Reports of inflammatory cell infiltration of the myenteric plexus (including eosinophilic or lymphocytic ganglionitis in several reports) [75-78] or muscle have been described in the literature; however, it is unclear whether antiinflammatory therapy is efficacious in reversing the inflammation, and it is still unclear whether the presence of inflammatory infiltration represents cause or effect of CIPO [73,79,80]. Decreased numbers of myenteric and submucosal neurons with increased interganglionic distance correlated with the severity of symptoms and clinical manifestations of deranged intestinal motility [81].

Mitochondrial neurogastrointestinal encephalopathy has been reported to be associated with altered ICCs [82].

TREATMENT

The basic principles of management of chronic intestinal pseudo-obstruction (CIPO) are based predominantly upon clinical experience [83].

Patients should be managed by a multidisciplinary team including a gastroenterologist, nutritionist, and transplant surgeon with experience in the treatment of CIPO [84].

Patients with CIPO require supplemental nutritional support. Prokinetics may be useful for acute and chronic therapy of intestinal pseudo-obstruction. Antibiotics are recommended in patients with small bowel bacterial overgrowth. Immunomodulator therapy should be reserved for patients with CIPO due to an established underlying inflammatory neuropathy. Surgery should be performed, if necessary, to provide access for venting/feeding. Surgery to resect or bypass localized disease of the small bowel should be avoided. Intestinal transplantation is indicated in selected patients in whom long-term parenteral nutrition cannot be initiated or continued safely. Treatment should also be directed at the underlying disease. As an example, enzyme replacement therapy has been associated with alleviation of gastrointestinal manifestations in patients with Fabry disease. (See "Fabry disease: Treatment and prognosis".)

Nutritional support — Early intervention with nutritional support is important, particularly for those who have had recurrent vomiting or reduced oral intake. Small meals consisting of liquid or homogenized foods are better tolerated than solids. Hypercaloric liquid formulations should be used in patients with low caloric intake. Oral or enteral nutrition is typically used for neuropathic disorders or in patients in whom the motility disorder is localized to the stomach and duodenum. Endoscopic access to the stomach with a jejunum extension tube may provide an effective means for decompression and enteral nutrition [85]. Parenteral nutrition may be necessary for patients with severe dysmotility (usually myopathic pseudo-obstruction). In a large multi-center experience of home parenteral nutrition (PN) for pediatric patients, the main complications were catheter-related bloodstream infections (1.7/1000 days of PN) and intestinal failure-associated liver disease (20 percent of cohort). Patients in the cohort with CIPO were not at greater risk that other indications [86]. However, patients with CIPO on TPN appear to have lower final heights and body weight Z-scores, and there may be micronutrient deficiencies transiently while receiving PN [87]. (See "Nutrition support in critically ill patients: An overview".)

Among adults requiring long term TPN, even up to 20 years after starting treatment, patients with Crohn disease, mesenteric ischemia, and CIPO were associated with a better overall survival than scleroderma and radiation enteritis [88].

Prokinetic agents — Prokinetic agents, particularly erythromycin and cisapride, may be useful for acute and chronic therapy of intestinal pseudo-obstruction, respectively [89]. However, these treatments are off-label, and risks and benefits should be discussed with the patient.

It is appropriate to combine a prokinetic agent with an antiemetic medication such as promethazine 12.5 to 25 mg twice daily (also available in liquid form or suppository) for symptom relief. The sedative effects of promethazine may be helpful when administered at bedtime. In patients who cannot tolerate promethazine, the 5-HT3 antagonist ondansetron 4 to 8 mg three times daily may be used. However, this class of medications delays colonic transit. (See "Characteristics of antiemetic drugs".)

Erythromycin — Intravenous erythromycin is effective during acute exacerbations of intestinal pseudo-obstruction, acting at least in part by stimulation of the motilin receptors [90,91]. Such patients are typically hospitalized and require intravenous

fluids. Intravenous erythromycin lactobionate at a dose of 3 mg/kg every eight hours should be continued for at least five to seven days.

Erythromycin has not been very effective for chronic therapy and has only been tried in a small number of patients [92]. Oral cisapride should **not** be given to patients receiving erythromycin, since there is a potential risk of drug interaction leading to significant arrhythmia (torsades de pointes). There is some evidence that intravenous erythromycin may be effective in patients with upper gut motility disorders due to scleroderma, but clinical experience is only anecdotal [93].

Prucalopride — Prucalopride, a 5HT4 receptor agonist, accelerates transit through the stomach, small bowel, and colon [94]. Prucalopride appears promising in the treatment of CIPO. In a randomized, double-blind, crossover study, prucalopride appeared to provide symptom relief in four of seven patients with CIPO. In three patients with visceral myopathy and one visceral neuropathy, 2 to 4 mg prucalopride (relative to placebo) significantly improved pain in three of four patients, nausea in two, vomiting in one, and bloating in four, whereas bowel function was not changed substantially [95]. In contrast to cisapride, prucalopride appears to have much lower risk of cardiac arrhythmia [96], even in the elderly [97], based on studies performed in patients with chronic constipation. The recommended dose of prucalopride in patients with CIPO is 2 mg daily in adults and 1 mg daily in those >65 years.

Cisapride — In randomized trials, oral cisapride at a dose of 20 mg three times a day was effective in improving gastric emptying but did not provide symptomatic relief in patients with CIPO [89,98-100].

However, in a randomized controlled trial in which 42 neuropathic patients (gastroparesis or intestinal dysmotility or CIPO) were randomized to cisapride at a dose of 10 or 20 mg three times daily or placebo for 12 weeks, overall symptom responses with cisapride were more likely in patients without coexisting vagal denervation [101].

Cisapride has been associated with a number of drug interactions and fatal cardiac arrhythmias, prompting the manufacturer to severely limit its availability in the United States, although it remains available in other countries. Prucalopride is typically used if a 5-HT4 receptor agonist is deemed appropriate for the management of the patient.

Metoclopramide — Intravenous metoclopramide is an alternative in patients with an acute exacerbation of intestinal pseudo-obstruction who cannot tolerate erythromycin. Metoclopramide may help initiate motility if the patient does not have prior evidence of adverse effects with metoclopramide and cannot tolerate erythromycin. Thus, metoclopramide may help during acute exacerbations at doses that are tolerated (usually 10 mg four times daily). A possible history of an extrapyramidal reaction to this agent should be elicited prior to beginning therapy. There is no evidence that metoclopramide is effective in the long-term treatment of pseudo-obstruction [102].

Octreotide — Patients with scleroderma may benefit from subcutaneous octreotide (a long-acting somatostatin analogue). A single study has reported success in treating five such patients with 50 mcg of octreotide administered subcutaneously at bedtime [103]. Octreotide caused an average of 3.6 migrating motor complexes (MMC) in three hours of small bowel recordings when there had previously been none. A similar benefit to intestinal motility with improvement in symptoms was observed in a few patients with idiopathic intestinal pseudo-obstruction, especially in combination with erythromycin [104]. However, it is important to be aware that when octreotide is administered during the daytime with meals, it significantly delays gastric emptying and small bowel transit of solids [105,106], which may be deleterious to patients with CIPO. Therefore, it is recommended that if octreotide is used in CIPO, it should be administered before bed, at least two hours after the last meal, and its main purpose is to induce MMCs and thereby reduce the risk of bacterial overgrowth in patients with CIPO.

Symptomatic improvement with octreotide may reflect changes in visceral afferent function rather than an effect upon transit through the intestine [107,108].

Anticholinestrerases — Case reports have suggested that acute exacerbation of intestinal pseudo-obstruction may respond to treatment with neostigmine (0.5 mg intramuscular or intravenous over five minutes with cardiac monitoring). If the patient has received mu-opiates, there may also be a response to subcutaneous methylnaltrexone (0.15 mg/kg). Case series in children suggest benefit from use of pyridostigmine in patients with severe intestinal dysmotility [109]. In adults with CIPO, treatment with pyridostigmine (starting at a dose of 10 mg twice daily and increasing from that dose) relieved symptoms and was safe [110].

Antibiotics — Patients with CIPO who have steatorrhea, vitamin B12 malabsorption, or folate excess may have bacterial overgrowth and should be treated empirically with antibiotics. (See "Small intestinal bacterial overgrowth: Management".)

Jejunal cultures are needed if steatorrhea does not respond to empiric antibiotics. Jejunal aspirate is the preferred test for diagnosing bacterial overgrowth in patients with CIPO as breath tests for bacterial overgrowth have a high false negative rate in patients with motility disorders [111]. The finding of $\geq 10^5$ aerobic colony forming units/mL in the jejunal aspirate (normal jejunal concentration is $\leq 10^4$ aerobic colony forming units/mL) is consistent with bacterial overgrowth. Antibiotics are rotated with drug-free intervals of at least 15 days in an attempt to avoid the development of bacterial resistance. In some patients with severe myopathic disease, it may be necessary to use "rotating" antibiotics (eg, week on, week off). (See "Small intestinal bacterial overgrowth: Management".)

A pilot study demonstrated safety of using serial frozen fecal microbiota transplantation, symptom relief (bloating, pain, and reduced intestinal dilatation on CT imaging) in selected patients with CIPO, and improvement in patient tolerance of enteral nutrition delivered via a naso-jejunal tube. Of note, 4 of the 9 patients had previously undergone ileostomy [112]. Additional studies are needed to validate these findings.

Immunomodulator therapy — Case reports have described intestinal pseudo-obstruction in association with lymphocytic infiltration of the myenteric plexus [1,113] or smooth muscle [114,115]. These observations suggest a potential role for immunomodulator therapy. Immunomodulator therapy should be reserved for patients with CIPO due to an underlying inflammatory neuropathy that is established by biopsy or by the presence of antineuronal antibodies (anti-Hu) [70]. The most common immunosuppressive agents used are methylprednisolone or prednisone starting at 40 to 60 mg daily. In one case report, paraneoplastic pseudo-obstruction in the setting of small cell lung cancer was reported to respond to rituximab and cyclophosphamide [116].

Cannabinoids — Symptomatic relief has been reported in patients treated with medical cannabis [117]. However, it is important to note that, in general, nonselective

cannabinoid receptor agonists generally inhibit gastrointestinal or colonic motility, and there are reports of intestinal intussusception with cannabis use [118].

Surgery — The role of surgery in the management of CIPO is to provide access to the stomach or small bowel for venting (decompression to relieve symptoms) and feeding, both of which may be performed laparoscopically. Enteral feeding may thus facilitate avoidance of total parenteral nutrition-related complications [119].

Resection of localized disease should be avoided in patients with CIPO. Clinical experience suggests that even though the disease may appear to be localized, it usually becomes evident in the remaining bowel, thereby rendering the benefits of a bypass temporary. Repeated surgery also leads to diagnostic confusion, making it difficult to distinguish CIPO from small bowel obstruction. Subtotal enterectomy for pseudo-obstruction has been performed for relief of severe pain associated with markedly distended loops of intestine. In such cases, the patient is committed to total parenteral nutrition for life as a consequence of surgery. Bypass of dilated segments has been suggested for patients with megaduodenum. However, in our experience, this procedure has been ineffective in patients with persistent symptoms.

Pacing of the intestine and electrical stimulation of the stomach or intestine are considered experimental at this time, although initial results have been favorable. (See "Electrical stimulation for gastroparesis".)

In general, non-transplant surgical management of CIPO should be avoided, as it is associated with high postoperative morbidity and mortality rates and frequent re-operation [120].

Percutaneous endoscopic colostomy — Colonoscopic insertion of a gastrostomy tube into the colon to relieve obstructive symptoms has been described in case reports. While the safety and long-term efficacy of this approach remain to be established, improvement in symptoms for up to two years has been reported [121].

Intestinal transplantation — Intestinal transplantation is indicated in patients in whom long-term parenteral nutrition cannot be initiated or continued safely. Intestinal transplantation for patients with motility disorders has been performed less frequently than for patients with short bowel syndrome.

Graft rejection, graft-versus-host disease, and immunosuppression-related lymphoproliferative disorders are more common with small intestinal transplantation than after other organ transplants [122,123]. However, the results of intestinal transplantation have improved over the past decade. As a result of surgical advances, control of acute cellular rejection, and a decrease in lethal infections, the rate of patient survival at one year now exceeds 90 percent at experienced centers.

Intestinal transplantation may be life-saving in children, but is indicated only in patients in whom long-term parenteral nutrition cannot be performed or continued safely including patients who develop liver complications due to parenteral nutrition, have difficult central line access, or have poor quality of life and worsening pain despite aggressive medical management [124-126]. Although autologous stem cell transplantation and liver transplantation have been used on patients with mitochondrial cytopathy, it is unclear if the benefits outweigh the risks [127,128]. (See "Overview of intestinal and multivisceral transplantation".)

In a study that evaluated long-term outcomes, predictors of survival, and risk of disease recurrence after gut transplantation (one-third with liver concomitantly transplanted, and two-thirds without liver) in 55 patients with CIPO, 42 percent children and 58 percent adults [129], patient survival was 89 percent at one year and 69 percent at five years with graft survival of 87 and 56 percent, respectively. Retransplantation was successful in 86 percent. Adults experienced numerically better patient and graft survival with lower incidence of posttransplant lymphoproliferative disorder and graft versus host disease. Initially restored nutritional autonomy was sustainable in 23 (70 percent) of 33 long-term survivors with improved quality of life. The remaining 10 recipients required reinstitution of home parenteral nutrition due to allograft enterectomy or gut dysfunction. In summary, gut transplantation is life-saving for patients with end-stage CIPO and HPN-associated complications. Long-term survival is achievable with better quality of life and low risk of disease recurrence.

PROGNOSIS

A number of clinical, histopathological, and manometric features have been identified as being predictive of outcomes in patients with chronic intestinal pseudo-obstruction (CIPO) (table 4) [130,131].

The long-term outcome is often especially poor in children, with 60 to 80 percent requiring parenteral nutrition and a mortality rate ranging from 10 to 40 percent [132-134].

In adults with CIPO, the vast majority of patients have evidence of nutritional compromise, and almost one-third require long-term home parenteral nutrition (HPN) [130]. Mortality rates of approximately 10 percent have been reported in adults, including HPN-related complications in 45 to 80 percent of cases [135].

In one series in adults that included 59 consecutive patients identified between 1985 and 2001 who were followed for a median of 4.6 years, symptoms associated with CIPO became progressively more severe with time [46]. Most patients had undergone a potentially dangerous surgery (mean 2.96 per patient) before a diagnosis was established, underscoring the need to recognize its presentation. Long-term outcomes were poor despite medical and surgical treatment. Approximately one-third of patients required long-term HPN, while about two-thirds had some nutritional limitation. Four patients underwent small bowel transplantation. Overall, 10 percent of patients died of disease-related complications.

Limited experience suggests that adults with CIPO and irreversible total parenteral nutrition complications benefit from isolated intestinal transplant (associated with different surgical techniques to empty the native stomach). In one study at a single institution; this strategy was reported to achieve good gastric emptying, with resumption of oral feeding and graft and patient survivals that are comparable to those associated with isolated intestinal transplant for short bowel syndrome [136].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Bowel obstruction".)

SUMMARY AND RECOMMENDATIONS

- Chronic intestinal pseudo-obstruction (CIPO) is a syndrome that suggests mechanical bowel obstruction of the small or large bowel in the absence of an anatomic lesion that obstructs the flow of intestinal contents. Segments of affected bowel appear dilated on radiography. (See 'Introduction' above.)

- Abdominal pain and distension are the most common clinical features. Patients may have diarrhea due to small bowel bacterial overgrowth. Nausea, vomiting, and weight loss are predominant symptoms in patients with CIPO involving the proximal gastrointestinal tract. Other features include anorexia, alternating bowel habits, and urinary symptoms. These symptoms may be acute, recurrent, or chronic. (See 'Clinical manifestations' above.)

- The diagnosis of CIPO is based on the presence of longstanding symptoms of obstruction in the absence of an anatomic cause of obstruction despite endoscopy and/or radiologic examination, and confirmation of impaired motility with scintigraphy. (See 'Diagnosis' above.)

- All patients should undergo laboratory testing to identify secondary causes of CIPO. (See 'Laboratory studies' above.)

  In patients with abnormal transit on scintigraphy and in whom there is a known underlying disease, no further investigation is necessary and appropriate therapy can be initiated. In patients with abnormal transit on scintigraphy and no known underlying disease, manometry should be performed. (See 'Identifying the etiology' above.)

  Autonomic testing is useful in patients with evidence of a neuropathic disorder on manometry, but without a known underlying neurologic disorder. (See 'Autonomic testing' above.)

- Nutritional support is important, particularly for those who have had recurrent vomiting or reduced oral intake. Small meals consisting of liquid or homogenized foods are better tolerated than solids. Hypercaloric liquid formulations should be used in patients with low caloric intake. Oral or enteral nutrition is typically used for neuropathic disorders or in whom the motility disorder is localized to the stomach and duodenum. Parenteral nutrition may be necessary for patients with

severe dysmotility (usually myopathic pseudo-obstruction). (See 'Nutritional support' above.)

- For patients with CIPO who have steatorrhea, vitamin B12 malabsorption, or folate excess (suggestive of bacterial overgrowth), we suggest empiric treatment with antibiotics (**Grade 2C**). Jejunal aspirate cultures are needed if steatorrhea does not respond to empiric antibiotics. Antibiotics, usually on a rotating basis, are used in patients who have confirmed small bowel bacterial overgrowth. (See 'Antibiotics' above.)

- For symptomatic relief in patients with CIPO, we suggest that prokinetic agents, particularly erythromycin for acute exacerbations of CIPO. For chronic symptoms of CIPO, we suggest cisapride or prucalopride (**Grade 2C**). (See 'Prokinetic agents' above.)

- Surgery should be performed to provide access to the stomach or small bowel for venting and feeding. Resection of localized disease should be avoided in patients with CIPO. (See 'Surgery' above.)

- Intestinal transplantation is indicated in patients in whom long-term parenteral nutrition cannot be initiated or continued safely. (See 'Intestinal transplantation' above.)

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Topic 2639 Version 19.0

GRAPHICS

Intestinal pseudo-obstruction in scleroderma

Barium radiograph in a patient with small bowel scleroderma and pseudo-obstruction syndrome reveals a dilated post-bulbar duodenum (megaduodenum) and jejunum, with infiltrated valvulae conniventes (arrow) in the lower jejunal loop.

Courtesy of Michael Camilleri, MD.

Graphic 65344 Version 4.0

Gastrointestinal motility disorders

Region	With dilatation	Without dilatation
Esophagus	Achalasia with mega-esophagus	Achalasia
Stomach	Acute gastric dilatation	Gastroparesis
Small bowel	Pseudo-obstruction	Chronic intestinal dysmotility
Colon	Megacolon/pseudo-obstruction	Slow transit constipation/colonic inertia

Graphic 73822 Version 1.0

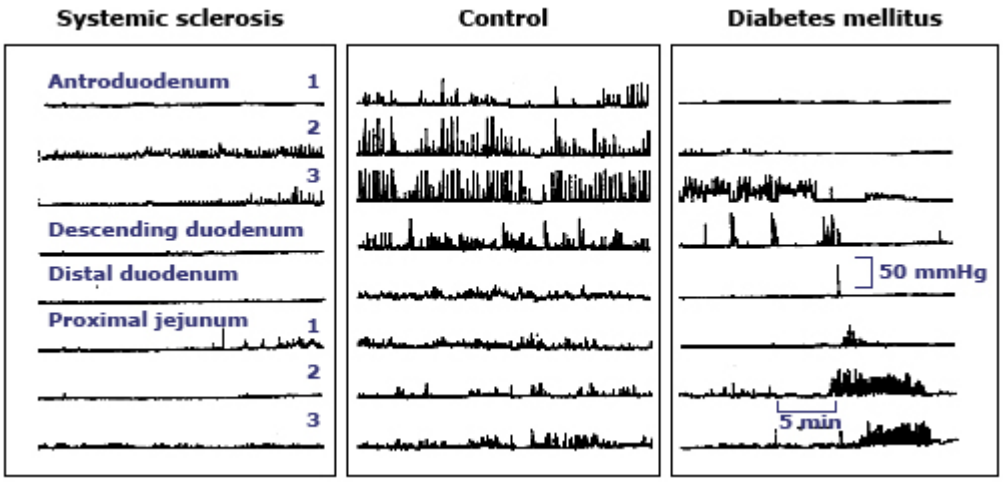
Main differences between mechanical versus functional intestinal obstruction

	Mechanical obstruction	POI	AIPO/ACPO	CIPO
Luminal obstruction	Yes	No	No	No
Motility	Initially ↑ then ↓ proximal to obstruction	↓	↓/uncoordinated	↓/uncoordinated
Dilatation	Yes (proximal to obstruction)	No	Yes	Yes
GI involvement	Proximal to obstruction	Mainly small bowel	Mainly colon	Pan-enteric
Radiology	Typical "cut-off" point; presence of air-fluid levels	"Cut-off point" occasionally present; air-fluid levels usually absent	"Cut-off point" occasionally present; air-fluid levels sometimes detected	"Cut-off point" occasionally present; air-fluid levels detectable
Course	Acute	Acute	Acute	Chronic
Progression	Rapidly evolving toward total obstruction	Self-limiting, slowly improving	May respond to medical treatment; major complication may occur	Variable, generally self-limiting
Treatment	Surgery	Supportive measures	Medical treatment (neostigmine); decompressive endoscopy or surgery in unresponsive cases	Variable; EN, TPN/HPN often needed

↑: increased; ↓: decreased; AIPO/ACPO: acute intestinal pseudo-obstruction/acute colonic pseudo-obstruction; CIPO: chronic intestinal pseudo-obstruction; EN: enteral nutrition; GI: gastrointestinal; POI: postoperative ileus; TPN/HPN: total/home parenteral nutrition.

Graphic 84010 Version 2.0

Manometry of the stomach and small intestine differentiates neuropathic and myopathic disorders

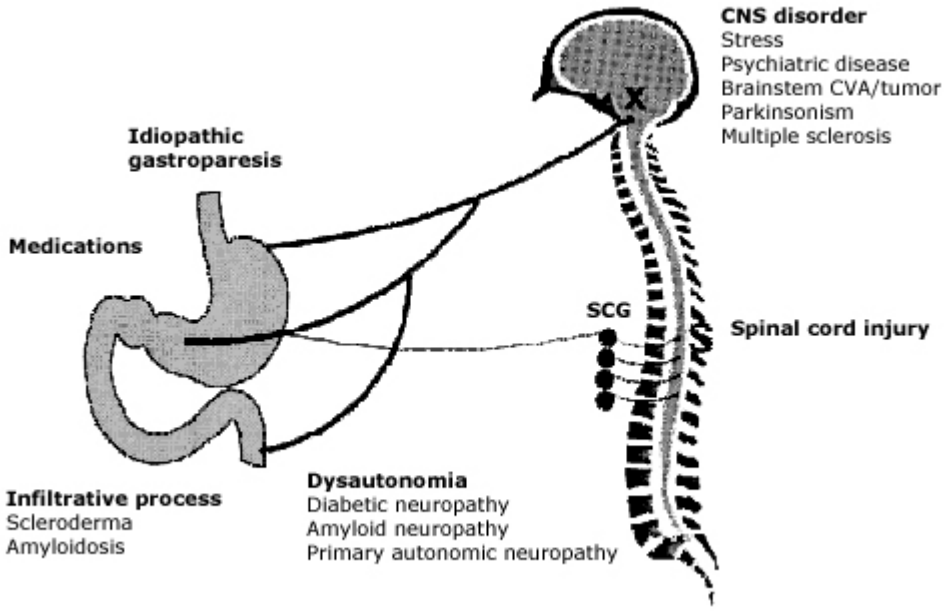


Postprandial gastrointestinal motility in a patient with systemic sclerosis (myopathic disorder, left panel) is characterized by low amplitude contractions at all levels compared with controls. By comparison, a neuropathic disorder such as diabetes mellitus (right panel) is characterized by normal contraction amplitude, but abnormal organization of the contractile response. Specifically, there is a lack of distal antral contractions, pyloric tonic, and phasic pressure activity, and persistence of migrating motor complex-like activity postprandially (proximal jejunum rows 2 and 3) despite the ingestion of a solid-liquid meal.

Adapted from: Camilleri M. Medical treatment of chronic intestinal pseudo-obstruction. Pract Gastroenterol 1991; 15:10.

Graphic 51540 Version 6.0

Neuromuscular disorders impairing gastric motor function



Several common neurologic disorders can affect gastrointestinal motility by altering the parasympathetic or sympathetic supply to the gut.

X: vagal nuceli; CNS: central nervous system; CVA: cerebrovascular accident; SCG: sympathetic chain ganglia.

Graphic 52708 Version 5.0

Commonly performed tests of autonomic function

Test	Principle	Nerves assessed
Sweat test	Heat stimulates thermoregulatory center	Central sympathetic adrenergic and peripheral sympathetic cholinergic
BP lying, standing	Postural BP control by adrenergic nerves	Sympathetic adrenergic
RR interval with deep breathing	Vagal reflux bradycardia	Cardiac vagus
Plasma pancreatic polypeptide response to modified sham feeding	Sham feeding stimulates vagal center and efferents	Efferent vagus to abdomen

Graphic 82750 Version 2.0

Prognostic factors in chronic intestinal pseudo-obstruction

Poor outcome	Good outcome
Myopathy	Gender (male)
Early/acute onset	No vagal dysfunction or sympathetic dysfunction
Urinary involvement	Clinical response to cisapride
Malrotation	Normal bowel diameter
Short bowel syndrome	Findings on small intestinal manometry: presence of MMCs, motor response to octreotide
Surgery	
Total parenteral nutrition (TPN)	
Findings on small intestinal manometry:	
Hypomotility	
Absence of MMCs	
Intestinal phasic and tonic pressure "bursts"	
Inadequate intestinal response to a meal (fed pattern)	

MMCs: migrating motor complexes.

Data from: Stanghellini V, Cogliandro RF, De Giorgio R, et al. Natural history of intestinal failure induced by chronic idiopathic intestinal pseudo-obstruction. Transplant Proc 2010; 42:15.

Graphic 86277 Version 1.0

Contributor Disclosures

Michael Camilleri, MD Equity Ownership/Stock Options: Dignify Therapeutics [Spinal cord injury]; Enterin [Constipation in Parkinson disease]. Patent Holder: Capsule for colonic transit by scintigraphy; 13C-mannitol for permeability measurement; Obesity-metabolomics to identify different phenotypes. Grant/Research/Clinical Trial Support: Takeda [Gastroparesis]; Novartis [Bile acid diarrhea]; Allergan [Bile acid malabsorption]; Vanda [Gastroparesis]; ILSI North America [Permeability]; Arena [Visceral pain in GI disorders]. Consultant/Advisory Boards: Ironwood [Gastroparesis]; Allergan [Diabetic gastroparesis]; AstraZeneca [Naloxegol and OIC]; ElobixAB [Bile acid inhibitor for constipation]; Takeda [Clinical trials]; AlfaSigma [Gastroparesis]; Bio-kier [Obesity, diabetes]; Shionogi [Opioid-induced constipation]; AEON Pharma [Gastroparesis]; Check-Cap [Capsule to measure GI and colonic motility]; Protagonist Therapeutics [IBS-diarrhea]; Arena [Visceral pain in GI disorders]; Kallyope [Obesity]; QED Therapeutics [Diarrhea]; Biokier [Diabetes]; OrbiMed [IBS-constipation]; Salix [Over-the-counter therapy for GI disorders]; Rose Pharma [IBS]; Allakos [Eosinophilic and mast cells GI disorders]; Ironwood [IBS]; EA Pharma [Gastroparesis and IBS]. **Lawrence S Friedman, MD** Employment (Spouse): Boston Health Care for the Homeless. Other Financial Interest: Elsevier; McGraw-Hill; Wiley [Gastroenterology]. **Shilpa Grover, MD, MPH, AGAF** Nothing to disclose
Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.
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