Chronic Intestinal Pseudo-Obstruction

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Paul E. Hyman and Nikhil Thapar

Chronic intestinal pseudo-obstruction (CIPO), far from a single entity, represents a heterogenous group of disorders affecting gut neuromuscular function. Such conditions are rare and vary in cause, severity, course, and response to therapy [1–6]. Most are severe, disabling and characterized by repetitive episodes or continuous symptoms and signs of bowel obstruction, including radiographic documentation of dilated bowel with air-fluid levels, in the absence of a fixed, lumen-occluding lesion [7]. At the present time, CIPO remains largely a clinical diagnosis based on phenotype, rather than pathology or manometry. The most common signs are abdominal distention and failure to thrive, and the most common symptoms are vomiting, constipation or diarrhea and abdominal pain. Heterogeneity in pseudo-obstruction includes, but is not limited to, a wide spectrum of abnormal gastric, small intestinal, and colonic myoelectrical activity and contractions as well as histologic abnormalities in nerve and muscle. The genetics for most CIPO conditions is poorly characterized. Although these diseases have distinctive pathophysiologic characteristics, they are considered together because of their clinical and therapeutic similarities (See Table 22.1 for list of heterogeneity).

P.E. Hyman, M.D. (✉)
Gastroenterology Division, Children's Hospital, Louisiana State University, 200 Henry Clay Ave, New Orleans, LA 70118, USA
e-mail: paulhyman@aol.com

N. Thapar, B.Sc.(hon), B.M.(hon), M.R.C.P., M.R.C.P.C.H., Ph.D.
Gastroenterology Unit, University College London, Institute of Child Health, Division of Neurogastroenterology and Motility , London, UK

Department of Paediatric Gastroenterology, Great Ormond Street Hospital for Children, London, UK

Etiology

CIPO may occur as a primary disease or as a secondary manifestation of a large number of other conditions that transiently (e.g., hypothyroidism, phenothiazine overdose) or permanently (e.g., scleroderma, amyloidosis) alter bowel motility (Table 22.2) [8–40].

Most congenital forms of neuropathic and myopathic CIPO are both rare and sporadic. There is no family history of pseudo-obstruction, no associated syndrome, and no evidence of other predisposing factors such as toxins, infections, ischemia, or autoimmune disease. Such conditions are likely to represent new mutations. More rarely, CIPO appears to show familial inheritance and a number of genes have been implicated. This is discussed in detail elsewhere in the book. Briefly, there are reports of autosomal-dominant [41, 42] and -recessive [43–46] neuropathic, and dominant [47, 48] and recessive [49, 50] myopathic patterns of inheritance. In the autosomal-dominant diseases, expressivity and penetrance are

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Table 22.1 Features of chronic intestinal pseudo-obstruction in pediatric patients

Onset
Congenital
Acquired
Acute
Gradual
Presentation
Megacystis—microcolon intestinal hypoperistalsis syndrome
Acute neonatal bowel obstruction, with or without megacystitis
Chronic vomiting and failure to thrive
Chronic abdominal distention and failure to thrive
Cause
Sporadic
Familial
Toxic
Ischemic
Viral
Inflammatory
Autoimmune
Area of involvement
Entire gastrointestinal tract
Segment of gastrointestinal tract
Megaduodenum
Small bowel
Colon
Pathology
Myopathy
Neuropathy
Lymphocytic or eosinophilic ganglionitis
Absent neurons
Immature neurons
Degenerating neurons
Absent cells of Cajal
Intestinal neuronal dysplasia
No microscopic abnormality

variable; some of those affected die in childhood, but those less affected are able to reproduce. An X-linked recessive form of neuropathic pseudo-obstruction has been mapped to its locus, Xq28 [51]. A recessive form of CIPO is described in mitochondrial neurogastrointestinal encephalopathy (MNGIE) [52]. When counseling families, a thorough family history is essential, and screening tests of relatives should be considered to seek milder phenotypic expression.

CIPO may result from exposure to toxins during critical developmental periods in utero. A few children with fetal alcohol syndrome [52] and a few exposed to narcotics in utero have neuropathic forms of CIPO. Presumably, any substance

Table 22.2 Causes of secondary acute, subacute, and chronic intestinal pseudo-obstruction in children

Toxic
Ketamine
Carbamazepine
Clonidine
Atropine and other anticholinergics
Theophyllin
Fludarabin
Vinblastin and other vinca alkaloids
Neuroleptics
Antidepressants
Phenothiazine
Opiates
Calcium channel blockers
Fetal alcohol syndrome [8]
Metabolic
Electrolyte imbalance (hypo K^+, hyper Mg^{2+}, hypo Ca^{2+}) [9]
Hypothyroidism
Hypoparathyroidism
Carnitine deficiency [10]
Vitamin E deficiency ("brown-bowel syndrome") [11, 12]
Infectious
Viral: CMV [13], EBV [14, 15], Herpes Zoster [16], Rotavirus [17]
Trypanosoma cruzei (young adults)
Lyme disease [18]
Immune
Celiac disease
Systemic sclerosis [19]
Lupus (myopathy) [20]
Autoimmune leiomyositis [21, 22]
Autoimmune enteric ganglionitis (with anti-enteric neurons antibodies, anti-PCNA antibodies) [23, 24]
Guillain-Barré syndrome [25]
Tumoral
Neural crest cell tumor: neuroblastoma, ganglioneuroblastoma [26]
Pheochromocytoma [27]
Thymoma (with anti-acetylcholine receptor antibodies) [28]
Striated myopathy
Myotonic dystrophy [29, 30]
Duchenne muscular dystrophy [31]
Desmin myopathy [32]
Mitochondrial myopathy [33, 34]
Central or peripheral generalized neuropathy
Degenerative process: diabetes, amyloidosis (not reported in children)
Mitochondrial neurogastrointestinal encephalopathy (MNGIE) [35]
Familial dysautonomia [36]
Acquired cholinergic dysautonomia or acquired pandysautonomia [37]

(continued)

Table 22.2 (continued)

Miscellaneous
Angioedema [38]
Postradiation enteropathy [39]
Kawasaki [40]

that alters neuronal migration or maturation might affect the development of the enteric plexuses and cause CIPO.

Children with chromosomal abnormalities or syndromes may suffer from pseudo-obstruction. Children with Down syndrome have a higher incidence of Hirschsprung's disease than the general population and may have abnormal esophageal motility [53] and neuronal dysplasia in the myenteric plexus. Rare children with Down syndrome have a myenteric plexus neuropathy so generalized and so severe that they present with pseudo-obstruction. Children with neurofibromatosis, multiple endocrine neoplasia type IIB, and other chromosome aberrations and autonomic neuropathies may suffer from neuropathic constipation. Children with Duchenne's muscular dystrophy sometimes develop pseudo-obstruction, especially in the terminal stages of life [54]. Esophageal manometry and gastric emptying are abnormal in Duchenne's dystrophy, suggesting that the myopathy includes gastrointestinal smooth muscle even in asymptomatic children [31]. Acquired pseudo-obstruction may be a rare complication of infection from cytomegalovirus [13] or Epstein-Barr virus [14]. Most recently, JC virus (JCV) a polyomavirus that can infect brain glial cells to cause severe illness has been shown to be present in the myenteric plexuses of adult patients with CIPO. JCV in enteroglial cells suggested a pathological role for this virus in enteric neuropathy [55]. This is yet to be shown in pediatric CIPO. Immunocompromised children and immunosuppressed transplant recipients seem at higher risk than the general population for acquired myenteric plexus neuropathy. Acquired CIPO might result from myenteric plexus neuritis from persistent viral infection or an autoimmune inflammatory response. Mucosal inflammation causes abnormal motility. With celiac disease [56], Crohn's disease, and the chronic enterocolitis associated with Hirschsprung's disease some patients develop dilated bowel and symptoms due, not to anatomic obstruction, but to a neuromuscular disorder presumably related to the effects of inflammatory mediators on mucosal afferent sensory nerves or motor nerves in the enteric plexuses. Other causes of CIPO associated with inflammation include myenteric neuritis associated with antineuronal antibodies [23] and intestinal myositis [22, 57].

Pathology (See Chap. 17)

There may be histologic abnormalities in the muscle or nerve or, rarely, both [58]. More recently there have also been descriptions of CIPO due to mesenchymopathies or deficiencies in interstitial cells of Cajal [59]. Assessment of such pathology in motility disorders is not standardized and therefore mesenchymopathy as a distinct entity remains unclear [24]. Histology is normal in about 10% of cases that are studied appropriately, although there is great variability in available expertise and protocols. Moreover, it is often difficult to determine what changes are primary, and what changes in nerve cell dropout and muscle fibrosis are caused by chronic distension and consequent ischemia. Recent initiatives are attempting to address this variability [60–62]. In cases of normal gross neuromuscular histopathology there may be an abnormality in neuronal diversity (subtype dropout) or some biochemical aspect of stimulus-contraction coupling.

When laparotomy is imminent for a child with pseudo-obstruction, there must be timely communication between the surgeon and the pathologist. Although a laparotomy is not generally undertaken for biopsy alone, increasing expertise with laparoscopy has facilitated it's use for the assessment of histopathology where confirmation is required prior to definitive surgery or to inform prognosis. When surgery is indicated (e.g., for colectomy, cholecystectomy, or creation of an ileostomy) a plan should be made to obtain a full-thickness bowel biopsy specimen at least 2 cm in diameter. As discussed in Chap. 17 the tissues

should be processed for routine and specialized histopathology studies including H&E, tinctorial stains, immunohistochemistry (IHC) and also for enzyme histochemistry and electron microscopy.

Muscle disease may be inflammatory but more often is not. In light microscopy of both familial and sporadic forms of hollow visceral myopathy, the muscularis appears thin. The external longitudinal muscle layer is more involved than the internal circular muscle, and there may be extensive fibrosis in the muscle tissue. By electron microscopy there are vacuolar degeneration and disordered myofilaments.

Neuropathic disease used to be examined with silver stains of the myenteric plexus [63, 64] and routine histologic techniques but the former has largely been superceded by IHC. The presence of neurons in the submucous plexus of a suction biopsy specimen eliminates Hirschsprung's disease as a diagnostic possibility but is inadequate for the evaluation of other neuropathies. There may be maturational arrest of the myenteric plexus. This hypoganglionosis is characterized by fewer neurons, which may be smaller than normal. Apart from abnormal development phenotypes other pathologies include neuronal degeneration, inflammation, and inclusion bodies. Maturational arrest can be a primary congenital disorder or can occur secondary to ischemia or infection. Changes can be patchy or generalized.

Intestinal neuronal dysplasia [65], or hyperganglionosis, is a histologic diagnosis defined by these findings: (1) hyperplasia of the parasympathetic neurons and fibers of the myenteric (and sometimes submucous) plexus, characterized by increases in the number and size of ganglia, thickened nerves, and increases in neuron cell bodies; (2) increased acetyl cholinesterase-positive nerve fibers in the lamina propria; (3) increased acetylcholine esterase-positive nerve fibers around submucosal blood vessels; (4) heterotopic neuron cell bodies in the lamina propria, muscle, and serosal layers. The first two criteria are obligatory.

Children with intestinal neuronal dysplasia are a heterogeneous group. Children with primary pseudo-obstruction due to neuronal dysplasia may have disease that is limited to the colon or disseminated. Other children may have neuronal dysplasia associated with prematurity, protein allergy, chromosome abnormalities, MEN IIB, and neurofibromatosis; however, intestinal neuronal dysplasia is an occasional incidental finding in bowel specimens examined for reasons unrelated to motility. Intestinal neuronal dysplasia correlates poorly with motility-related symptoms [66]. Thus, a pathologic diagnosis of intestinal neuronal dysplasia neither predicts clinical outcome nor influences management.

Clinical Features

Presentation

More than half the affected children develop symptoms at or shortly after birth. A few cases are diagnosed in utero, by ultrasound findings of polyhydramnios and megacystis and marked abdominal distention. Intestinal malrotation is found in both neuropathic and myopathic congenital forms of pseudo-obstruction. Of children who present at birth, about 40% have an intestinal malrotation. In the most severely affected infants symptoms of acute bowel obstruction appear within the first hours of life. Less severely affected infants present months later with symptoms of vomiting, diarrhea, and failure to thrive. A few patients have megacystis at birth and insidious onset of gastrointestinal symptoms over the first few years. More than three quarters of the children develop symptoms by the end of the first year of life, and the remainder present sporadically through the first two decades.

Although there is individual variation in the number and intensity of signs and symptoms, it may be useful to note the relative frequencies in this population (Table 22.3). Abdominal distention and vomiting are the most common features, complaints of about three quarters of the patients. Constipation, episodic or intermittent abdominal pain, and poor weight gain are features in about 60% of cases. Diarrhea is a complaint in one third. Urinary tract smooth muscle is affected in those with both hollow visceral neuropathy and hollow visceral myopathy, about one fifth of all

Table 22.3 Clinical symptoms in children with chronic intestinal pseudo-obstruction

Study	Abdominal distension	Vomiting	Constipation	Failure to thrive	Abdominal pain	Diarrhea	Dysphagia
Faure et al. [1] $n=105$	100	94	70	64	46	29	9
Vargas et al. [2] $n=87$	73	50	51	23	NA	21	2
Granata et al. [3] $n=59$	59	31	27	NA	NA	26	NA
Schuffler et al. [4, 5] $n=30$	23	19	20	15	NA	16	NA
Heneyke et al. [6] $n=44$	31	40	31	NA	NA	–	NA
Total $n=325$	286 (88%)	234 (72%)	199 (61%)	102 (31%)	–	92 (28%)	11 (3%)

NA not available

pseudo-obstruction patients. Often these children are severely affected at birth and are described by the phenotype *megacystis-microcolon intestinal hypoperistalsis syndrome* [2].

The majority of children's clinical course is characterized by relative remissions and exacerbations. Factors that precipitate deteriorations include intercurrent infections, general anesthesia, psychological stress, and poor nutritional status.

The radiographic signs are those of intestinal obstruction, with air-fluid levels, dilated stomach, small intestine, and colon, or microcolon in those studied because of obstruction at birth [6]. There may be prolonged stasis of contrast material placed into the affected bowel, so it is prudent to use a nontoxic, isotonic, water-soluble medium to prevent barium from solidifying. Children who feel well still show radiographic evidence of bowel obstruction. The greater problem arises when children develop an acute deterioration. Radiographs demonstrate the same patterns of bowel obstruction that are seen when the child feels well. In children who previously had surgery, it can be difficult to discriminate between physical obstruction related to adhesions and an episodic increase in CIPO symptoms.

Diagnosis

An incorrect CIPO label can result from misdiagnosis of infant and toddler victims of pediatric illness falsification, known in the United Kingdom as Fabricated or Induced Illness, formerly known as Münchausen's syndrome by proxy [67]. Well-meaning clinicians inadvertently cocreate disease as they respond to a caretaker's symptom fabrications by performing tests and procedures, including parenteral nutrition support, repeated surgery, and even small bowel transplantation [68]. Adolescents with disabling abdominal pain arising from psychiatric diseases such as pain disorder, posttraumatic stress disorder, and Asperger's syndrome may also confuse gastroenterologists [69]. A differential diagnosis for CIPO is provided in Table 22.4.

Table 22.4 Differential diagnosis of CIP in children

Aerophagia
Gastroparesis
Functional constipation
Cyclic vomiting syndrome
Chronic abdominal pain with psychological dysfunction (pain-associated disability syndrome)
Bacterial overgrowth of various origins (lactase deficiency, disaccharidase deficiency, intestinal duplication)
Aerodigestive fistula
Pediatric illness falsification (Munchausen-by-proxy syndrome, fabricated or induced illness imposed on a child)

Diagnostic testing provides information about the nature and severity of the pathophysiology. Manometric studies are more sensitive than radiographic tests to evaluate the strength and coordination of contraction and relaxation in the esophagus, gastric antrum, small intestine, colon, and anorectal area.

In affected children scintigraphy demonstrates delayed gastric emptying of solids or liquids and reflux of intestinal contents back into the stomach. Dilated loops of bowel predispose to bacterial

overgrowth, so breath hydrogen testing may reveal elevations in fasting breath hydrogen and a rapid increase in breath hydrogen with a carbohydrate meal.

Esophageal manometry is abnormal in about half those affected by CIPO. In children with myopathy, contractions are low amplitude but coordinated in the distal two-thirds of the esophagus. Lower esophageal sphincter pressure is low, and sphincter relaxation is complete. When the esophagus is affected by neuropathy, contraction amplitude in the esophageal body may be high, normal, low, or absent. There may be simultaneous, spontaneous, or repetitive contractions [70, 71]. Relaxation of the lower esophageal sphincter may be incomplete or absent.

Antroduodenal manometry findings are always abnormal with intestinal pseudo-obstruction involving the upper gastrointestinal tract; however, manometry is often also abnormal in partial or complete small bowel obstruction. Although the manometric patterns of true obstruction differ from those of CIPO in adults [72, 73], such a distinction is not always clear. Contrast radiography and, as a last resort, exploratory laparotomy are best for differentiating true obstruction from pseudo-obstruction. Antroduodenal manometry should not be used as a test to differentiate true bowel obstruction from pseudo-obstruction. Manometry may help to determine the physiologic correlates for the symptoms, to assess drug responses, and for prognosis [70, 74–76]. Intestinal myopathy causes low-amplitude coordinated contractions, and neuropathy causes uncoordinated contractions [77]. Pain with each high-amplitude antral contraction suggests gastric hyperalgesia. Interpretation of antroduodenal manometry requires recognition of normal and abnormal features (Table 22.5).

The abnormalities in pseudo-obstruction are commonly discrete and easily interpreted by eye (see Chap. 9). They contrast markedly with normal features of antroduodenal manometry.

In most cases the manometric abnormality correlates with clinical severity of the disease. For example, children with total aganglionosis have contractions of normal amplitude that are never organized into migrating motor complexes (MMCs), fed patterns, or even bursts or clusters of contractions but are simply a monotonous pattern of random events. Children with such a pattern are dependent on total parenteral nutrition (TPN). More than 80% of children with MMCs are nourished enterally, but more than 80% of children without MMCs require partial or total parenteral nutrition [75].

Table 22.5 Antroduodenal manometric features from studies of 300 children

Normal features
Migrating motor complex (MMC) (fasting)
Postprandial (phase 2-like) pattern
Abnormal features in duodenum
Absent MMC phase 3
Sustained tonic contractions
Retrograde propagation of phase 3
Giant single-propagating contractions
Absent phase 2 with increased phase 3 frequency
Persistently low-amplitude or absent contractions
Prolonged nonpropagating clusters
Postprandial abnormalities
Antral hypomotility after a solid nutrient meal
Absent or decreased motility
Failure to induce a fed pattern (MMC persists)

[a]Each of these features is recognized by visual inspection of the recording. From Tomomasa T, DiLorenzo C, Morikawa A, et al. Analysis of fasting antroduodenal manometry in children. Dig Dis Sci. 1996;41:195–203.

Normal antroduodenal manometry and absence of dilated bowel in a patient with CIPO symptoms shifts the emphasis from medical to psychological illness [78]. It is often difficult for families to consider and engage in psychological intervention, especially when the decision is based on a "lack of medical findings." Thus it is important to interpret the antroduodenal manometry as a positive prognostic indicator, *especially* when the results are normal.

Colon manometry is abnormal in colonic pseudo-obstruction [79]. The normal features of colon manometry in children include (1) high-amplitude propagating contractions (phasic contractions stronger than 60 mmHg amplitude) propagating over at least 30 cm; (2) a gastrocolic response (the increase in motility that follows a meal); and (3) an absence of discrete abnormalities.

With neuropathic disease contractions are normal or reduced in amplitude, but there are no high-amplitude propagating contractions or gastrocolic response. With myopathy there are usually no colonic contractions (see Chap. 10).

There are several pitfalls with intestinal and colonic manometry. In dilated bowel no contractions are recorded and manometry is not diagnostic. Recordings filled with respiratory and movement artifacts from agitated, angry, crying patients are uninterpretable. Acute pseudo-obstruction is usually associated with ileus, so that an absence of contractions may not reflect the underlying abnormality. Manometry is most likely to be helpful when performed in a cooperative patient at a time when the patient is feeling well. Anorectal manometry is usually normal in CIPO. There is an absence of the rectoinhibitory reflex only in Hirschsprung's disease and in some patients with intestinal neuronal dysplasia. In a few specialized centers, electrogastrography is a noninvasive screening test for evaluation of children thought to have CIPO [80]. Skin electrodes are placed over the stomach, just as surface electrodes are placed over the heart to perform electrocardiography. The electrical slow-wave rhythms of the gastric body and antrum are recorded. Gastric slow waves normally occur at a rate of 3 per minute. Gastric neuropathies are characterized by decreases (bradygastria) or increases (tachygastria) in slow-wave frequency. Gastric myopathies are characterized by reduced power, a measure of signal amplitude.

Treatment

Nutrition Support

The goal of nutrition support is to achieve normal growth and development with the fewest possible complications and the greatest patient comfort. In children with CIPO, motility improves as nutritional deficiencies resolve and worsens as malnutrition recurs.

Roughly a third of affected children require prolonged periods of partial or total parenteral nutrition (TPN). One third require total or partial tube feedings, and the rest eat by mouth. In those with intestinal neuropathies about 30% need TPN. In those with enteric myopathies over 70% need TPN. TPN is the least desirable means of achieving nutritional sufficiency because of the potential for life-threatening complications. In the absence of enteral nutrients, the gastrointestinal tract does not grow or mature normally. In the absence of the postprandial rise in trophic and stimulant gastrointestinal hormones, bile stasis and liver disease develop [81]. TPN-associated cholelithiasis [82] and progressive liver disease are important causes of morbidity and mortality in children with pseudo-obstruction. The minimal volume, composition, and route of enteral support required to reverse or prevent the progression of gastrointestinal complications have not been determined. It seems likely that a complex liquid formula containing protein and fat, given by mouth or gastrostomy tube, and contributing 10–25% of the child's total calorie requirement would be sufficient to stimulate postprandial increases in splanchnic blood flow and plasma concentrations of gastrin and other trophic factors. Every effort should be extended to maximize enteral nutritional support in parenteral nutrition-dependent children.

Continuous feeding via gastrostomy or jejunostomy may be effective when bolus feedings fail. Most children with visceral myopathy and a few with neuropathy have an atonic stomach and almost no gastric emptying. In these children, a feeding jejunostomy may be helpful for the administration of medications and for drip feedings [83]. Care must be taken to place a jejunostomy into an undistended bowel loop.

Drugs

Drugs to stimulate intestinal contractions are helpful in a minority of children with CIPO. Bethanechol, neostigmine, metoclopramide, and domperidone have not been useful. Perhaps the best documented benefit of pharmacoptherapy for CIPO has come from serotonergic drugs. The combined 5HT4 agonist and 5HT3 antagonist

cisapride's mechanism of action is to bind to serotonin receptors on the motor nerves of the myenteric plexus, facilitating release of acetylcholine and stimulating gastrointestinal smooth muscle contraction. It appeared most likely to improve symptoms in children with MMCs and without dilated bowel [84] and acted by increasing the number and strength of contractions in the duodenum of children with CIPO. It did not initiate the MMC in patients without it or inhibit discrete abnormalities. Cisapride was withdrawn from the commercial marketplace in much of the world in the early 2000s because of concerns related to rare fatal cardiac arrhythmias. In the USA today cisapride is available at no cost to individual patients after successful application to the Federal Drug Administration for an Investigational New Drug application, and approval by a local Human Subjects Committee. The pure 5HT4 agonist tegaserod held similar promise for CIPO, but was also withdrawn for cardiovascular concerns similar to those about cisapride. Newer serotonergic agents are being tested but their effect in CIPO is not yet studied.

Erythromycin, a motilin receptor agonist, appears to facilitate gastric emptying in those with neuropathic gastroparesis by stimulating high-amplitude 3-min antral contractions, relaxing the pylorus, and inducing antral phase 3 episodes in doses of 1–3 mg/kg intravenously [85] or 3–5 mg/kg orally. Erythromycin does not appear to be effective for more generalized motility disorders [85], is ineffective for stimulating colonic contractility [86].

Octreotide, a somatostatin analogue, given subcutaneously, induces small intestinal phase 3-like clustered contractions and suppresses phase 2 [87]. However, the clusters may not propagate, or may propagate in either direction and intestinal transit and nutrient absorption are optimal during phase 2. Augmentin, a combination of amoxacillin and clavulinate, increases contractions in the small bowel [88]. Augmentin may be useful in selected CIPO cases to increase the contractions and treat bacterial overgrowth.

Antibiotics are used for bacterial overgrowth. Bacterial overgrowth is associated with steatorrhea, fat-soluble vitamin malabsorption, and malabsorption of the intrinsic factor—vitamin B_{12} complex. It is possible that bacterial overgrowth contributes to bacteremia and frequent episodes of central venous catheter-related sepsis and to TPN-associated liver disease. Bacterial overgrowth, mucosal injury, malabsorption, fluid secretion, and gas production may contribute to chronic intestinal dilatation, which may further impair motility. Chronic antibiotic use may result in the emergence of resistant strains of bacteria or overgrowth with fungi. Thus, treating bacterial overgrowth must be considered on an individual basis.

Excessive gastrostomy drainage may result from retrograde flow of intestinal contents into the stomach or from gastric acid hypersecretion. Gastric secretory function or gastric pH should be tested before beginning antisecretory drugs. Histamine H_2-receptor antagonists may be used to suppress gastric acid hypersecretion. Tolerance develops after a few months of intravenous use [89], so the drug should be given orally when possible. When a drug is added to TPN, gastric pH should be assessed at regular intervals to monitor drug efficacy. Induction of achlorhydria is inadvisable because it promotes bacterial overgrowth in the stomach.

Constipation is treated initially with oral polyethylene glycol solutions, suppositories, or enemas. Oral lavage solutions often cause abdominal distention because of delayed small bowel transit in children with pseudo-obstruction. For constipation and small bowel disease, cecostomy or appendicostomy may simplify management by bypassing the small bowel [90]. If colon manometry shows no colon contractions, the most efficient course is ileostomy and colon resection. An ileostomy takes the resistance of the anal sphincter out of the system, and facilitates flow of chyme from the higher pressures from gastric contractions to the absence of pressure at the stoma.

Acute pain due to episodes of pseudo-obstruction is best treated by decompressing distended bowel. Opioids are rarely needed if the bowel is promptly decompressed. It is appropriate to consider nonsteroidal anti-inflammatory agents (e.g., ketorolac)

and epidural anesthetics as alternatives to, or in combination with, systemic opioids.

Chronic pain can be a problem in children with congenital pseudo-obstruction and is common in adolescents who have autoimmune or inflammatory disease and progressive loss of intestinal function. Pain consists of a nociceptive component and an affective component. Patients with chronic pain benefit from a multidisciplinary approach including not only attention to gastrointestinal disease but also mental health assessment and treatment for the affective pain component. Collaboration with pain management specialists is beneficial for optimizing the care of pseudo-obstruction patients who complain of chronic pain. Multiple modalities for pain relief are useful: cognitive behavioral therapy, massage, relaxation, hypnosis, psychotherapy, yoga, and drugs all have shown positive effects. Drugs that reduce afferent signaling, improving chronic visceral pain, include the tricyclic antidepressants, clonidine, and gabapentin [91]. Opioid use is inadvisable, because opioids disorganize intestinal motility, tolerance to opioids develops rapidly, and opioid withdrawal can simulate the visceral pain of acute pseudo-obstruction.

Sympathetic plexus neurolysis, by interrupting sympathetic efferent (and inhibitory) activity on upper digestive tract, improved symptoms in CIPO patients [92–94].

Surgery

One of the management challenges in pseudo-obstruction is the evaluation and reevaluation of newborns and children with episodic acute obstructive symptoms. Although most acute episodes represent pseudo-obstruction, it is important to intervene with surgery when the episode is a true bowel obstruction, appendicitis, or another surgical condition. Many children with episodes of acute pseudo-obstruction undergo repeated exploratory laparotomies. It is important to avoid unnecessary abdominal surgery in children with pseudo-obstruction for several reasons: (1) They often suffer from prolonged postoperative ileus: (2) Adhesions create a diagnostic problem each time there is a new obstructive episode: (3) Adhesions following laparotomy may distort normal tissue planes and make future surgery riskier in terms of bleeding and organ perforation. After several laparotomies turn up no evidence of mechanical obstruction, the surgeon may choose a more conservative management plan for subsequent episodes, including pain management, nutritional support, and abdominal decompression.

Gastrostomy was the only procedure that reduced the number of hospitalizations in adults with pseudo-obstruction [95], and the experience with children seems to be similar [96]. Gastrostomy provides a quick and comfortable means of evacuating gastric contents and relieves pain and nausea related to gastric and bowel distention. Continued "venting" may decompress more distal regions of small bowel, precluding nasogastric intubation and pain medication. Gastrostomy is used for enteral feeding and enteral administration of medication. Gastrostomy placement should be considered for those receiving parenteral nutrition and for children who will need tube feedings longer than 2 months. In many patients, endoscopic gastrostomy placement is ideal. In those with contraindications to endoscopic placement, surgical placement is appropriate. Care must be taken to place the ostomy in a suitable position, above the gastric antrum in the midbody.

Fundoplication is rarely indicated for pseudo-obstruction. After fundoplication, symptoms change from vomiting to repeated retching [97]. In children with pseudo-obstruction, vomiting is reduced by venting the gastrostomy. Acid reflux is controlled with antisecretory medication.

Results of pyloroplasty or Roux-en-*Y* gastrojejunostomy to improve gastric emptying in pseudo-obstruction have been poor; gastric emptying remains delayed. Altering the anatomy rarely improves the function of the dilated fundus and body. Small bowel resections or tapering operations may provide relief for months or even years; however, when the lesion is present in other areas of bowel those areas gradually dilate and symptoms recur.

Ileostomy can decompress dilated distal small bowel and provide further benefit by removing

from the circuit the high-pressure zones at the end of the bowel namely the colon and the anal sphincter. Transit of luminal contents is always from a high-pressure zone to a lower-pressure one. In pseudo-obstruction patients with gastric antral contractions but no effective small bowel contractions, bowel transit improves with the creation of an ileostomy because of the absence of resistance to flow at the ostomy site.

Colectomy is sometimes necessary in severe congenital pseudo-obstruction to decompress an abdomen so distended that respiration is impaired. In general, colon diversions are inadvisable because of a high incidence of diversion colitis [98]. Diversion colitis can cause abdominal pain, tenesmus, hematochezia and may worsen motility of the proximal intestine as chemical by-products of inflammation circulate to vulnerable tissues.

Subtotal colectomy with ileoproctostomy cures rare children with neuropathic pseudo-obstruction confined to the colon. Typically these children are able to eat normally and grow, but they are unable to defecate spontaneously. They differ from children with functional constipation in that their stools are never huge or hard, there is no retentive posturing, the history of constipation begins at birth, and there are often extrarectal fecal masses. Colon pathology may show neuronal dysplasia, maturational arrest, or no diagnostic abnormality, but colon manometry is always abnormal, without high-amplitude propagating contractions or a postprandial rise in motility index. Before colectomy for constipation, antroduodenal manometry may be necessary to determine whether the upper gastrointestinal tract is involved. Abnormal antroduodenal manometry is a relative contraindication to colectomy because upper gastrointestinal symptoms appear after colon resection [99]. Before surgery, a psychological evaluation may help to assess the possibility of psychiatric disease and somatization masquerading as colon disease and to prepare the patient for the procedures.

A cecostomy using a small "button" ostomy appliance for regular infusion of colonic lavage solution has not been effective for severe colonic pseudo-obstruction. The abdomen distends, but the colon does not empty.

There is increasing experience with the pacemakers in gut motility disorders although the experience is limited to gastroparesis, not CIPO [100].

Failed medical management may signal a need for total bowel resection. Rarely, a mucosal secretory disorder complicates the management of pseudo-obstruction. Several liters of intestinal secretions drain from enteric orifices each day. When secretions cannot be controlled with loperamide, anticholinergics, antibiotics, steroids, or somatostatin analogue, it may be necessary to resect the entire bowel to avoid life-threatening electrolyte abnormalities and nutritional disturbances caused by the large volume losses. Total bowel resection may reduce episodes of bacterial transmigration across dilated bowel to eliminate repeated life-threatening central venous catheter infections [101]. Total bowel resection should be considered alone or in combination with small bowel transplantation. Small bowel or combined liver–bowel transplants have the potential to cure children with pseudo-obstruction. Transplant results in CIPO children are similar to results in children undergoing transplantation for short bowel syndrome or intractable diarrhea [102]. (See also Chap. 46.)

Outcomes

The prognosis of children with CIPO remains guarded, with risk of mortality as high as 30% in the first year of life. Complications of parenteral nutrition are the cause of death in a majority of children [103, 104]. Thus, TPN is life saving, but measures to avoid TPN and, once started, to discontinue TPN are appropriate. Children with lower socioeconomic status tend to be on TPN longer than children from high socioeconomic status, suggesting that those with better health care access are aggressively moved away from parenteral nutrition [103]. The quality of life for surviving children with pseudo-obstruction and their families is

reduced compared to others with chronic disease [103]. The factors responsible for reduced quality of life in CIP were chronic pain and the caretaker's time commitment for participating in their child's medical care [103]. Adverse prognostic factors include early onset disease, enteric myopathies, associated malrotation, and absent phase 3 of the migrating motor complex on small intestinal manometry. A few children with congenital neuropathic CIPO improve with time. Several factors may be responsible. First, caloric needs are greatest in the first year, and decrease in subsequent years. Thus, the infant who can digest 50% of his or her caloric needs in the first year, may have no change in motility, but digest 100% of his or her lessening caloric needs in subsequent years. Second, motility may improve spontaneously. The mechanisms for improvement in this small group are unexplained.

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