Current Gastroenterology Reports (2019) 21: 70
https://doi.org/10.1007/s11894-019-0737-y

PEDIATRIC GASTROENTEROLOGY (S ORENSTEIN AND S KHAN, SECTION EDITORS)

Pediatric Intestinal Pseudo-obstruction in the Era of Genetic Sequencing

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Published online: 17 December 2019

Abstract

Purpose of Review The purpose of this review is to discuss current knowledge on pediatric intestinal pseudo-obstruction. We will also review new mutations that have been identified through advancement in genetic testing, allowing for a better understanding of the underlying mechanisms of intestinal dysmotility and potential etiologies.

Recent Findings With the advancements in genetic testing, new mutations have been identified in the diagnosis of megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS), a disorder leading to pediatric pseudo-obstruction. MYLK, LMOD1, MYL9, and MYH11 encode for various proteins within smooth muscle cells; abnormalities within these proteins lead to abnormal intestinal smooth muscle contractions.

Summary Chronic intestinal pseudo-obstruction (CIPO) is defined by symptoms of bowel obstruction in the absence of a lumen-occluding lesion. CIPO is a heterogeneous group of disorders caused by abnormalities in the enteric neurons, intestinal smooth muscle, and/or the interstitial cells of Cajal (ICC). Symptoms can be non-specific and etiologies include both primary and secondary causes of CIPO that contribute to the delay in recognizing this condition and making the correct diagnosis. Chronic intestinal pseudo-obstruction has been recognized in both adults and children with fundamental differences in the etiology, symptom onset, clinical features and natural history of this disorder. For this reason, it has been considered a separate entity referred to as pediatric intestinal pseudo-obstruction (PIPO).

Keywords Intestinal pseudo-obstruction · Gastrointestinal motility · Manometry

Abbreviations

MMIHS	Megacystis-microcolon-intestinal hypoperistalsis syndrome
CIPO	Chronic intestinal pseudo-obstruction
PIPO	Pediatric intestinal pseudo-obstruction
ICC	Interstitial cells of Cajal
ENS	Enteric nervous system
MMC	Migrating motor complex
MNGIE	Mitochondrial neurogastrointestinal encephalomyopathy
CREN	Constant rate enteral nutrition
SIBO	Small intestinal bacterial overgrowth

This article is part of the Topical Collection on *Pediatric Gastroenterology*

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Introduction

Chronic intestinal pseudo-obstruction is heterogeneous group of disorders characterized by symptoms of intestinal obstruction without evidence of a lumen-occluding lesion. Abnormalities in the enteric neuromusculature in combination or in isolation lead to enteric neuropathy (extrinsic or intrinsic), enteric myopathy, and/or mesenchymopathies (abnormalities in the interstitial cells of Cajal (ICC) network) causing various degrees of abnormal gastrointestinal motility [1]. Chronic intestinal pseudo-obstruction has been recognized in both adults and children with fundamental differences in the etiology, symptom onset, clinical features, and natural history of this disorder. For this reason, it has been considered a separate entity referred to as pediatric intestinal pseudo-obstruction (PIPO) [2]. In this review, we will focus on

PIPO. We will review new mutations that have been identified through advancement in genetic testing, which allow for a better understanding of the underlying mechanisms of intestinal dysmotility and potential etiologies. We will discuss the etiologies, underlying mechanisms leading to abnormal motility, diagnosis, and possible treatments.

This condition was first described in adults in the mid-twentieth century by Dudley and colleagues. In 1958, they identified 13 patients who presented with symptoms mimicking intestinal obstruction. They underwent exploratory laparotomy, but no lumen occluding lesion was found and they applied the term intestinal pseudo-obstruction in adults [3]. Nearly 20 years later, in 1977, Byrnes and colleagues described 11 pediatric patients with chronic idiopathic intestinal pseudo-obstruction, their clinical characteristics, and prognosis [4]. At that time, a family pedigree was completed and an autosomal dominant pattern of inheritance with variable penetrance was suggested but no gene mutation was identified. It was not until the twenty-first century that specific gene mutations were identified as potential causes of gastrointestinal dysmotility [5]. PIPO should be considered in a child who has symptoms mimicking intestinal obstruction but without evidence of a lumen-occluding lesion. The diagnosis of PIPO requires 2 of the following 4 criteria: (1) objective measurement of small bowel neuromuscular involvement with manometry, histopathology or transit studies; (2) recurrent and/or persistently dilated loops of small bowel with air fluid levels; (3) genetic or metabolic abnormalities identified which have previously been reported in PIPO; (4) inability to tolerate oral feedings to maintain growth and development (requires supplemental enteral or parenteral nutrition support) [2]. The study of gastrointestinal motility disorders has gained significant interest in the recent years. NAPSGHAN has identified thirty-eight motility centers across North America in 20 states and Canada offering manometry testing [6]

Epidemiology

PIPO is a rare and complex disorder. In 2018, diagnostic criteria were proposed by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition with a goal to improve diagnosis, management and treatment while decreasing morbidity and mortality in these patients. Until recently, due to a lack of conformity, few epidemiological studies reporting the incidence and prevalence in the pediatric population have been reported. Data from the American Pseudo-obstruction and Hirschsprung Society (now part of the International Foundation for Functional Gastrointestinal Disorders) suggest that less than 100 infants are born every year in the USA with primary PIPO [7]. In 2014, a nationwide Japanese survey reported an estimated pediatric prevalence of 3.7 in 1 million individuals less than 15 years of age. More than half of the children (56.5%) diagnosed with PIPO developed symptoms in the neonatal period (< 1 month old), 19.4% within infancy (1–12 months old), 14.5% in childhood (1–7 years of age), and 9.7% in school age or later (7–15 years of age) [8].

Etiology

PIPO can be divided into primary, secondary and idiopathic etiologies. Primary disorders leading to PIPO are defined as abnormalities within the development, degeneration, or inflammation of the enteric neuromusculature. These disorders include sporadic or familial forms of myopathy, neuropathy, mesenchymopathy (abnormal ICC network), mitochondrial diseases, or neuropathy associated with multiple endocrine neoplasia type IIB (Table 1) [9–14, 15••, 16–24, 25•].

Conditions leading to an inflammatory neuropathy such as lymphocytic and eosinophilic ganglionitis or leiomyositis of the neuromusculature can also affect gastrointestinal motility. Though few of these conditions have been reported in the literature, they are a very important category of disorders as they are amendable to treatment.

Autoimmune enteric leiomyositis is characterized by the histopathological finding of dense lymphocytic infiltrate of the muscularis propria mainly consisting of cytotoxic T cells on full-thickness biopsies of the small intestine. Patients typically present in infancy to early childhood with motility disturbances of the small and large intestine with elevated autoantibodies on laboratory findings. Of the six pediatric cases reported in the literature, two patients reached complete remission on immunosuppressive therapy [26, 27].

Eosinophilic myenteric ganglionitis is characterized by the histopathological finding of eosinophilic infiltration within the mucosa, submucosa, and myenteric plexus on full thickness biopsies of the small intestine. Patients typically present from neonatal period to childhood with progressive abdominal distension and obstruction. In contrast to autoimmune enteric leiomyositis, all four patients reported in the literature responded well to dietary changes and immunosuppressive therapy [28, 29].

Four types of anti-neuronal autoantibodies have been reported in the literature: ANNA-1 (or Anti-Hu), anti-VGCC (anti-voltage gated calcium channel) antibodies, anti-ganglionic acetylcholine receptor antibodies, and anti-Yo antibodies [30]. They are often associated with an underlying disease (commonly a paraneoplastic syndrome) or idiopathic forms of myenteric ganglionitis [31]. Auto-antibodies are suspected to arise from an autoimmune response to a paraneoplastic syndrome; however, anti-Hu antibodies have been identified in cases without evidence of a neoplastic disorder. It has been postulated that these antibodies could arise from parasitic infections, such as trypanosomiasis (Chagas

Table 1 Primary PIPO with identified genetic mutations

Gene	Syndrome	Function	Inheritance	Phenotype	Age of onset
Sox 10 [9]	Type IV Waardenburg syndrome	Sporadic	Autosomal dominant	Peripheral neuropathy with hypomyelination, sensorineural deafness and pseudo-obstruction	Neonatal period
POLG1 (DNA-polymerase gamma) [10, 11]	Congenital myopathy and gastrointestinal pseudo-obstruction	Encodes for the catalytic subunit of the mitochondrial DNA	Autosomal recessive	Associated with mitochondrial depletion and deletions. Severe hypotonia and generalized muscle weakness, severe abdominal distension and hypoactive bowel	Neonatal period
FLNA (filamin A) [12]	Chronic idiopathic intestinal pseudo-obstruction (CIIPX)	Encodes large cytoskeletal proteins	X-linked recessive	Abnormal filamin A leads to cytoskeletal abnormalities and potentially disrupts enteric-neuron structure and function. Seizures and progressive abdominal distension and obstruction	Neonatal period
L1CAM (L1 cell adhesion molecule) [13]	Hydrocephalus with stenosis of the aqueduct of Sylvius (HSAS) and congenital idiopathic intestinal pseudo-obstruction	Encodes a transmembrane glycoprotein involved in neurite outgrowth and neuronal migration	Autosomal recessive	Defect in the differentiation of the interstitial cells of Cajal leading to progressive distension and intermittent episodes of obstruction	Neonatal period
ACTG2 (enteric smooth muscle actin–gamma 2) [14]	Familial visceral myopathy; megacystis-microcolon-intestinal hypoperistalsis syndrome	Encodes enteric smooth muscle Actin	Autosomal dominant, sporadic	Altered ACTG2 protein in the muscularis propria leads to impaired contractility	Neonatal-3rd decade in life
MYH11 (myosin heavy chain 11) [15••, 16, 17]	Megacystis-microcolon-intestinal hypoperistalsis syndrome)	Encodes myosin light chain	Autosomal recessive	Abnormal MYH11 in smooth muscle myosin leads to impaired contractility	Neonatal-3rd decade in life
MYLK (myosin light chain kinase) [18]	Megacystis-microcolon-intestinal hypoperistalsis syndrome	Encodes a kinase required for myosin activation and subsequent interaction with actin filaments	Autosomal recessive	Abnormal MYLK leads to impaired smooth muscle cell contraction	Neonatal-3rd decade in life
LMOD1 (leiomodin 1) [19]	Megacystis-microcolon-intestinal hypoperistalsis syndrome	Encodes visceral smooth muscle cells	Sporadic	Abnormal LMOD1 leads to impaired intestinal smooth muscle contractility	Neonatal-3rd decade in life
MYL9 (myosin regulatory light chain 9) [20]	Megacystis-microcolon-intestinal hypoperistalsis syndrome	Encodes a regulatory myosin light chain	Autosomal recessive	Abnormal MYL9 leads to impaired intestinal smooth muscle contractility	Neonatal-3rd decade in life
RET proto-oncogene (receptor tyrosine kinase) [21, 22]	MEN2B	Expressed in the neural crest cells of the enteric ganglia and encodes a member of the receptor tyrosine kinase family of transmembrane receptors	Autosomal dominant	Gain in function mutation associated with intestinal ganglioneuromas leading to increased cell number in the myenteric plexus and dysmotility	Infancy to 3rd decade of life
TYMP (thymidine phosphorylase) [23]	Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)	A nucleoside which maintains adequate thymidine in mitochondria	Autosomal recessive	Accumulation of thymidine in mitochondrial DNA leads to impaired function. Multi-system mitochondrial disease with	Infancy–3rd decade of life

Table 1 (continued)

Gene	Syndrome	Function	Inheritance	Phenotype	Age of onset
				progressive gastrointestinal dysmotility	
RAD21 [24]	Mungan syndrome	Part of a cohesion complex that controls pairing and unpairing in cell replication. Plays an important role in epithelial and neuronal survival and ABOP regulation in the gastrointestinal tract	Autosomal recessive	Pseudo-obstruction, megaduodenum, long segment Barrett's esophagus and cardiac abnormalities	1st–2nd decade of life
SGOL1[25•]	Chronic atrial and intestinal dysrhythmia (CAID)	Component of the cohesion pathway	Autosomal recessive	Accelerated cell cycle progression and enhanced activation of TGF-B signaling leading to changes in both the enteric nervous system and smooth muscle	1st to 4th decade of life

disease), which could explain the neuronal degeneration leading to esophageal achalasia and megacolon [32, 33]

Secondary causes of PIPO may include a variety of conditions affecting the intestinal smooth muscle, enteric neurons, and/or the ICC network. Multiple systemic illnesses can have an impact on the gastrointestinal tract including rheumatological, endocrinological, and metabolic conditions [1, 2]. Other conditions such as infections, toxins, and autonomic nervous system abnormalities affect the enteric nervous system. Idiopathic PIPO is defined when a primary or secondary etiology has not been identified. It is imperative that when a child presents with symptoms suggestive of PIPO, a thorough history and physical exam is completed to rule out secondary causes of PIPO that may have a potential treatment (Table 2) [1].

Pathology

PIPO can be further classified into neuropathy, myopathy, mesenchymopathy and mixed (combined neuropathy, myopathy, and mesenchymopathy) based on where the abnormalities are found within the gastrointestinal tract, enteric neurons, intestinal smooth muscle, the ICC network or combined enteric neurons, smooth muscle, and ICC network, respectively. Pathologic abnormalities of the enteric neuromusculature have been under investigation for the past 70 years [34]. The diagnosis of these conditions requires special care and standardization in addition to consideration of the age of the patient, durations of symptoms, and other underlying or associated abnormalities [35]. In 2009, the Gastro International Working Group presented guidelines for histological techniques and reporting, along with a classification of gastrointestinal neuromuscular pathology at the World Congress of Gastroenterology in London, UK. The goal of this project was to create diagnostic standardization of gastrointestinal neuromuscular disorders and their underlying histopathological abnormalities to improve diagnosis and provide better prognostic and therapeutic information to families [36]. In 2018, the ESPGHAN-led expert group recommended obtaining full-thickness intestinal biopsies for histopathological analysis if a patient were to undergo surgery to improve symptoms and potentially reduce the number of acute pseudo-obstructive events [2]. Although previous studies report a higher incidence of post-operative ileus and adhesion formation in patients undergoing surgery with PIPO, new literature suggests that patients with PIPO can undergo full-thickness intestinal biopsies safely using modern laparoscopic techniques for diagnostic purposes alone [37, 38]. In 2008, Knowles et al. completed a prospective study performing 124 laparoscopic-assisted full thickness intestinal biopsies in adult patients with clinico-physiological diagnoses of chronic intestinal pseudo-obstruction, enteric dysmotility, and severe irritable bowel syndrome. Eight percent of patients

Table 2 Secondary cause of PIPO

Conditions affecting the smooth muscle
Rheumatology
Dermatomyositis/polymyositis
Scleroderma
Systemic lupus erythematous
Connective tissue and skeletal muscle disorders
Duchenne muscular dystrophy
Myotonic dystrophy
Ehlers Danlos syndrome
Conditions affecting the enteric nervous system
Neurofibromatosis
Familial dysautonomia
Primary dysfunction of the autonomic nervous system
Diabetes neuropathy
Fetal alcohol syndrome
Post-viral related inflammatory neuropathy
Cytomegalovirus
Epstein-Barr virus
Varicella Zoster virus
JC virus
Herpes simplex virus
Chagas disease
Endocrine
Diabetes
Thyroid dysfunction
Hypoparathyroidism
Pheochromocytoma
Metabolic
Porphyria
Electrolyte imbalances (potassium, magnesium, calcium)
Drugs
Antidepressants
Perinatal zidovudine
Vinca alkaloids
Calcium channel blockers
Cyclopentolate/phenylephrine eye drops
Miscellaneous
Post-neonatal necrotizing enterocolitis neuropathy
Gastroschisis
Celiac disease
Crohn's disease
Radiation injury
Kawasaki disease
Major trauma/surgery
Paraneoplastic syndrome

Adapted from, "Rudolph, Colin D. et al. Diagnosis and treatment of chronic intestinal pseudo-obstruction in children: report of consensus workshop. Journal of Pediatric Gastroenterology and Nutrition 1997." [1]

experienced obstructive symptoms but minimal other morbidity and no mortality. Overall, specific diagnostic yield for adult patients with PIPO was 81%, being high for jejunal biopsies (89%) but low for ileal and colonic biopsies. Laparoscopic assisted full-thickness intestinal biopsies appears to be a safe and effective procedure to achieve additional diagnostic information with jejunal biopsies achieving the highest diagnostic yield [39].

Enteric Neuropathy

The gastrointestinal tract consists of an extensive intrinsic nervous system called the enteric nervous system (ENS). The ENS is composed of two major ganglionated plexuses, myenteric (Auerbach's) and submucosal (Meissner's), which are connected through reflex circuits and can function independently of the central nervous system, but is not autonomous [40]. The ENS is a highly-integrated system interacting with the enteric reflex circuits in addition to reflexes that pass from the gut through the central nervous system and back and reflexes that pass through the sympathetic ganglia [41]. The ENS is viewed as a "mini-brain" with a library of preset motor patterns in the small and large intestine that are seen during fasting, the post-prandial period and emesis and can be identified by antroduodenal manometry studies. In normal physiology, the motor activity of the antrum and small intestine is characterized by patterns of organized muscular contractions during the fasting and post-prandial periods. This motor activity during fasting is composed of three phases that together make up the inter-digestive migrating motor complex (MMC). The purpose of the MMC is to clear debris, secretions, and microbes preventing bacterial overgrowth. The MMC cycles throughout the day and usually lasts for 50–180 min (Fig. 1) [42]. The presence of a normal MMC during fasting and the change to a fed pattern after ingestion of a test meal indicates intact enteric neuromuscular function. The ENS also controls other gut functions including secretion, absorption, and vascular tone via interactions with the endocrine system. Due to the significant impact the ENS has on gastrointestinal function, abnormalities can lead to a variety of digestive problems and decreased quality of life.

Neuropathic PIPO is typically caused by a loss of enteric neurons or due to an inflammatory neuropathy within the enteric ganglia and/or neuronal connections. Other conditions affecting the extrinsic nervous system can also influence the ENS leading to abnormal gastrointestinal functioning. Enteric neuropathies are classified into primary and secondary neuropathies (Table 3) [43]. Long-term outcomes and prognosis for neuropathic PIPO are better than for myopathic PIPO [37].

Enteric Myopathy

Normal intestinal peristalsis requires an intact smooth muscle layer called the muscularis propria. The smooth muscle is composed of two distinct layers. The inner layer is composed of circular muscle, with thick bundles of smooth muscle cells oriented parallel to the intestinal wall. The outer layer is composed of longitudinal muscle characterized by stroma of collagen and elastin fibers containing thin bundles of smooth muscle cells perpendicular to the intestinal wall. Contraction of the circular musculature and relaxation of the longitudinal musculature allow for peristalsis of the digestive tract. The

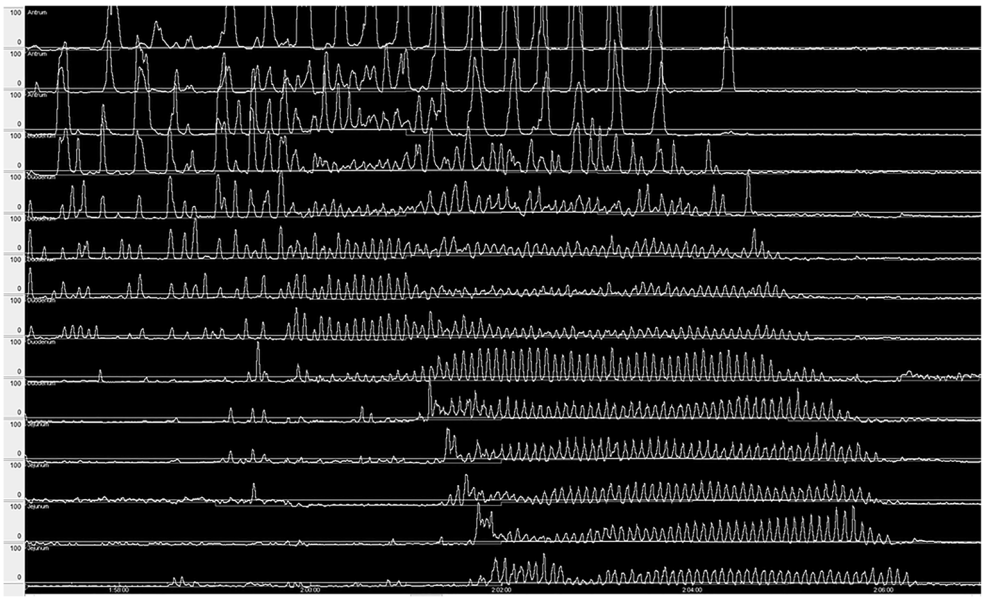

Fig. 1 Phases I–III are depicted in the tracing. Phase I is quiescent followed by phase II which has increased phasic contractions and finally phase III which is an organized motor pattern with antegrade propagation. Abnormalities within the MMC indicate abnormal enteric neuromusculature. This figure was taken from Dr. Soods personal library

myenteric plexus is located between these two layers of smooth muscle. Most of the motor neurons that innervate the circular and longitudinal smooth muscle layers reside within this myenteric plexus [44]. Abnormalities within the smooth muscle layer can be found within the distribution and morphology of smooth muscle cells. Enteric myopathies can be further classified into primary and secondary enteric myopathies (Table 4) [43].

Enteric myopathies differ from enteric neuropathies for the following reasons. (1) They typically present in infants and children and are congenital and/or genetic in the majority of cases. (2) They present with severe visceral dilatation and often with other organ involvement. (3) Long-term outcomes and prognosis are poor [37, 45].

Mesenchymopathies

Mesenchymopathies are abnormalities within the ICC network. ICC are found throughout the gastrointestinal track from the esophagus to the internal anal sphincter. They are found as distinct networks or interspersed between muscle cells in various regions from the submucosa to the subserosa. There appear to be three distinct types of ICC identifiable on electron microscopy by the expression of surface CD117 (c-Kit) protein which is a membrane receptor with tyrosine kinase activity. They have variable characteristics including the presence of intermediate filaments, mitochondria, gap junctions, caveolae, and basal lamina that seem to determine the specific function of each type of cell. At least four separate functions of ICC have been identified. (1) ICC are electrically active cells coupled to smooth muscle cells which conduct a slow wave that is thought to be responsible for the pacemaker activity of the intestinal smooth muscle cells. (2) They mediate cholinergic and nitrergic neurotransmission. (3) They determine smooth muscle membrane potential and gradient. (4) They appear to be involved in mechanotransduction [46, 47]. Abnormalities within the number of ICC or the integrity of the ICC networks can lead to PIPO in infants and children [48–51].

Table 3 Classification of enteric neuropathies

Primary neuropathies
Abnormal developmental phenotypes
Degenerative neuropathies
Neuropathies with inflammation
Inclusion body neuropathies
Other neuronal findings
Secondary neuropathies
Systemic disorders
Local disorders

Table 4 Classification of enteric myopathies

Primary myopathies
Abnormal developmental (morphogenic) phenotypes
Myopathies with vacuolation, atrophy and fibrosis
Myopathies with inflammation
Inclusion body myopathies
Other smooth muscle findings
Secondary myopathies
Systemic disorders
Local disorders

Mixed Neuropathy, Myopathy and Mesenchymopathies

Due to the heterogeneous nature of PIPO, there can be more than one type of pathology found on histological examination. In mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), evaluation of intestinal tissues often reveal enteric myopathy, mainly atrophy and fibrosis of the external layer of the muscularis propria of the small intestine, and enteric neurogenic changes that involve the myenteric plexus and ganglion cells. Changes in mitochondrial morphology, including abnormally shaped and large mitochondria in the smooth muscle cells of the small intestine, and ganglion cells of the entire GI tract have been reported. In addition to enteric myogenic and neurogenic changes, recent studies report absent ICC networks in MNGIE [52].

Clinical Features

The presentation of PIPO can vary based on the involvement of the gastrointestinal track. The most common presenting symptoms include abdominal distension followed by constipation, vomiting, and malnutrition. [8, 37, 53–55]. Recurrent and/or worsening episodes of pseudo-obstruction can be triggered by an inter-current illness, central line sepsis, general anesthesia, and psychological stress [37]. The majority of pediatric patients present during the neonatal period with a primary form of PIPO. In 2002, Mousa et al. reported a higher incidence (~ 60%) of enteric neuropathies compared to enteric myopathies in their cohort of 85 pediatric patients. Myopathic forms of PIPO have more frequent bladder involvement and significant morbidity compared to neuropathic forms. Additional predictors of poor outcome include < 1 years old at onset, intestinal midgut malrotation, short gut syndrome, inability to tolerate enteral feeds, and dependence on parenteral nutrition [37, 53]. The risk of mortality is approximately 20% of cases [53].

Signs and symptoms of malabsorption and malnutrition are frequent as enteral feeds exacerbate symptoms making oral feedings challenging. As a result of the intestinal stasis, small intestinal bacterial overgrowth (SIBO) is a common complication of PIPO and associated with worsening abdominal distention and pain. Nutritional complications can develop due to malabsorption and micronutrient deficiencies if the diagnosis is delayed and parenteral nutrition is not initiated.

Because of the non-specific nature of the symptoms associated with PIPO, the condition may go unrecognized for a long time and can be confused with other functional gastrointestinal disorders. Patients may be wrongly diagnosed with Munchausen's syndrome-by-proxy (also known as factitious disorder), or on the other hand, Munchausen's syndrome-by-proxy can mimic PIPO [56].

Diagnosis

PIPO should be suspected in patients who presents with symptoms of intestinal obstruction such as abdominal distension, vomiting, constipation, and malnutrition. The age at onset and a thorough history and physical exam are very important as these will direct the diagnostic work up for primary and secondary causes of PIPO. More than 50% of pediatric patients will present during the first month of life and up to 80% by the first year of life [37, 53–55]. Megacystis-microcolon-intestinal hypoperistalsis (MMIH) syndrome can be detected on antenatal ultrasound by an enlarged bladder in 88% of cases, with gastrointestinal symptoms presenting several months postnatal [57]. It is imperative to exclude a lumen-occluding lesion or malrotation in the differential diagnosis as this could be a potential surgical emergency. An upright abdominal radiograph is a simple and inexpensive first screening test to identify dilated loops of small bowel and air fluid levels which may suggest an obstruction [8]. Contrast studies play in important role in the initial work up for PIPO as they rule out the presence of a lumen-occluding lesion or intestinal malrotation. Water-soluble contrast is recommended in order to avoid possible concrete formation in the colon from the delayed passage of barium. In patients who cannot tolerate ingesting a large amount of contrast, or where an extra-luminal lesion is suspected, a computed tomography (CT) or magnetic resonance imaging (MRI) can also identify causes of intestinal obstruction.

Laboratory testing can be directed towards secondary causes of PIPO related to systemic diseases. These forms of PIPO are potentially reversible with treatment targeted at the underlying cause. Patients who are on parenteral nutrition due to malnutrition should also have frequent laboratory evaluations to monitor for electrolyte and micronutrient abnormalities. For patients presenting in the neonatal period, genetic testing may uncover a familial or sporadic gene mutation that can provide prognostic and therapeutic information to families (Table 5).

Manometry studies are used to evaluate the motor function and coordination of the esophagus, small intestine, colon, and anorectrum by measuring pressure changes within the lumen of the corresponding organ. They are particularly helpful in evaluation of the small intestine in the work up for PIPO because the small intestine is nearly always affected [53]. This can be challenging as the findings on antroduodenal manometry can be difficult to interpret and requires experience and training. In expert hands, manometry can be a useful adjunct tool to radiographic studies and provide detailed information regarding the strength and coordination of contractions in the gastrointestinal tract [45].

Antroduodenal manometry studies can aid in characterizing different types of PIPO. Enteric myopathies have low-amplitude and organized contractions, whereas enteric neuropathies have normal amplitude contractions and

Table 5 Laboratory work up

Screening evaluation
Complete blood cell count
Electrolytes
Liver enzymes
Albumin
Inflammatory markers (C-reactive protein and erythrocyte sedimentation rate)
Thyroid function test
Fasting cortisol
Exclude secondary causes of PIPO
Diabetes mellitus-serum glucose, hemoglobin-A1C
Celiac disease-anti-tissue transglutaminase IgA and total immunoglobulin A
Connective tissue and skeletal muscle disorders—anti-nuclear antibody, anti-double-stranded DNA, SCL-70, aldolase and creatine phosphokinase
Pheochromocytoma-urine catecholamines
Autoimmune conditions—anti-Hu and type1 anti-neuronal nuclear antibodies
Erythropoietic protoporphyria-urinary porphyrins
Infectious—serology for Chagas disease, EBV, CMV, JC virus, HSV and rotavirus
Metabolic—thymidine phosphorylase activity and serum lactic acid
Drugs or toxins—urine toxicology screen
Genetic screening should be completed in all patients with suspected PIPO and other congenital abnormalities or syndromic forms of the condition

unorganized or absent phase III of the MMC [53, 58]. Differentiating PIPO into neuropathic and myopathic etiologies based on manometry findings can be challenging. Careful interpretation is required as dilated loops of intestine can produce low amplitude contractions due to the inability of the catheter to register adequate pressures in the intestinal lumen. Subtle abnormalities during antroduodenal manometry studies can be difficult to interpret. Abnormal contraction patterns have been reported in partial and complete bowel obstruction which may be missed on imaging studies [59]. A normal antroduodenal manometry study and the absence of dilated loops of bowel essentially exclude the diagnosis of PIPO [60].

Additional studies, including esophageal, colonic, and anorectal manometries, can be utilized based on the presenting symptoms to determine which parts of the gastrointestinal tract are involved. In patients presenting with dysphagia, abnormal esophageal manometry may suggest foregut involvement [4, 55]. Chronic constipation has been reported in up to 70% of patients diagnosed with PIPO; therefore, colonic manometry can aid in determining the involvement of the colon and is required prior to consideration for isolated or multi-visceral transplantation for the most severe cases [54, 61]. Abnormalities found on colonic manometry include lack of a gastrocolic reflex and absence of high amplitude propagating contractions after administration of bisacodyl. This may be difficult to assess in the presence of colonic dilatation that can also show low amplitude or simultaneous contractions. Finally, the presence of a rectal inhibitory reflex found on anorectal manometry can rule out Hirschsprung disease in the setting of chronic constipation and a dilated colon.

Although manometry can be helpful to investigating the integrity of the enteric neuromusculature, it has several pitfalls. While inter-observer agreement for identifying phase III of the MMC on antroduodenal manometry has been reported as excellent, the inter-observer agreement varied for other subtle motor abnormalities [62]. Movement artifact in an uncooperative and crying child can make interpretation difficult. The ideal timing for manometry studies should be when the child has no acute illness and medications known to affect motility have been held.

Histopathologic evaluation is beneficial in the diagnosis and prognosis of patients with suspected PIPO. Guidelines for histopathological techniques and reporting for gastrointestinal neuromuscular pathology was proposed by the 2009 Gastro International working group in order to improve diagnoses and provide families with prognostic and therapeutic information [43]. Since PIPO can potentially affect the entire gastrointestinal tract full thickness biopsies of the gastric antrum, small intestine and colon should be obtained to identify histological abnormalities of the gastrointestinal neuromusculature. This is particularly important in conditions amendable to treatment with immunomodulation [26–29]. Recent studies in both adults and pediatrics, utilizing modern laparoscopic techniques, have proven safe and efficacious in obtaining adequate tissue samples for histological evaluation [63].

Treatment

The goal for treatment in PIPO is to optimize nutrition and growth while improving quality of life by minimizing surgical interventions and preserving any remaining intestinal motor function. Providing adequate nutrition can be challenging in these patients and often requires a combination of oral feedings with parenteral and enteral nutrition. Mousa et al. evaluated the long-term outcomes of 85 children with congenital intestinal pseudo-obstruction and showed that 53 (62%) patients were dependent on partial or total parenteral nutrition. Thirteen of those patients died from parenteral nutrition-related complications. The mortality rate for patients

diagnosed with PIPO is high ranging between 10 and 25% based on the age of presentation [37, 53, 54]. Parenteral nutrition-related complications account for a large percentage of deaths in these patients. Electrolytes and micronutrients should be monitored closely in patients on parenteral nutrition to avoid complications. Patients are particularly at risk during episodes of acute pseudo-obstructive events due to increased fluid losses via vomiting and gastric and/or ileostomy drainage. Optimizing enteral nutrition therapy and prioritizing discontinuation of parental nutrition is key to survival. Bolus or constant rate enteral nutrition (CREN) can provide enteral nutrition if patients do not tolerate bolus feeds through a nasogastric tube or gastrostomy tube. Children who have involvement of the stomach and small bowel can be fed by CREN directly into the proximal small bowel via a gastrojejunal or jejunostomy tube. The gastrostomy tube can also be a useful tool to vent the stomach and decompress the small bowel during episodes of severe pseudo-obstruction. Complete assessment of gastrointestinal function is important to potentially salvage small intestinal motor function and to determine appropriate surgical interventions. In patients with total colonic dysmotility on manometric studies, an ileostomy creation is beneficial to potentially delay or prevent further small intestinal dysmotility. For patients who have partial colonic dysmotility that does not respond to medical therapy, cecostomy formation for antegrade enemas has been shown to be helpful [64].

The main goal for using pharmacotherapy is to improve gastrointestinal motility, thereby improving oral feedings, limiting small intestinal bacterial overgrowth, and alleviating symptoms. Few medications have proven to significantly improve outcomes in children with PIPO, as the majority of these medications require an intact enteric nervous system to function. Erythromycin is a motilin receptor agonist that has been shown to stimulate antral contractions and induce phase III of the MMC in children who had an MMC during the fasting period [65]. Octreotide is a somatostatin analogue that has been shown to improve enteral feeding tolerance in children by stimulating phase III of the MMC on antroduodenal manometry studies [66, 67]. Amoxicillin-clavulanic acid was shown to induce duodenal phase III-like contractions of the MMC after administration directly into the small intestine [68]. Cisapride is a 5HT3 antagonist and 5HT4 agonist; it binds to the serotonin receptors in the myenteric plexus resulting in acetylcholine release and smooth muscle contractions. Cisapride has been shown to improve gastrointestinal motility in patients with PIPO by increasing post-prandial duodenal contractions [69, 70]. It is no longer available in the USA due to concerns of rare fatal cardiac arrhythmias, and its use requires an Investigational New Drug application from the Food and Drug Administration [71]. Pyridostigmine is an acetylcholinesterase inhibitor that improves gastrointestinal motility by increasing the availability of acetylcholine at the neuromuscular junctions of the myenteric plexus. In 2018, Manini et al. published a case series using oral Pyridostigmine in 4 patients with gastrointestinal motility disorders which was effective in all cases improving abdominal distension, bowel movement frequency, and enteral feeding tolerance [72].

SIBO is a common complication of in PIPO due to stasis of the small bowel that can lead to mucosal damage, malabsorption, increased fluid secretions, and gas production. It has been associated with steatorrhea, iron, fat-soluble vitamin (A, D, E, and K), and vitamin B12 deficiency [73]. Careful use of oral antibiotics is recommended and can help improve abdominal distension and pain. Commonly used antibiotics include amoxicillin-clavulanic acid, metronidazole, trimethoprim-sulfamethoxazole, and aminoglycosides. Rifaximin has minimal systemic absorption, and adult studies have shown clinical efficacy at improving hydrogen breath test results and symptoms of SIBO [74]. Repeated and prolonged use of oral antibiotics is associated with risk of emergence of antibiotic resistant organisms as well as yeast overgrowth. A recent study from China showed that mycotic infections were associated with increased mortality in children with PIPO; therefore, a combination of an anti-fungal compound and oral antibiotics should be considered [75].

Chronic abdominal pain caused by PIPO can be debilitating and decrease the quality in life for many children. The pain is characterized primarily by visceral pain due to mechanical stretching and distension of the gastrointestinal tract, thereby stimulating visceral nociceptors. Visceral pain is often poorly localized and felt at the midline [76]. The medications used in pediatrics for chronic pain are limited. Tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors have been shown to be effective in treating neuropathic pain in pediatric patients. Due to significant side effects, they should be started at a low dose and slowly titrated up until pain relief is established [77]. Gabapentin has been found to be effective in relieving pain in pediatric patients as an adjunct therapy or monotherapy [78]. Opioids should be avoided for the use of chronic pain in patients with PIPO due to their additive nature and adverse side effects of decreased intestinal motility. Children, with PIPO, are at risk of developing colonic volvulus due to significant colon dilatation. Prompt diagnosis and surgical intervention can be lifesaving in this situation. Differentiating colonic volvulus from an acute pseudo-obstruction crisis can be difficult as clinical symptoms and signs are similar [79].Collaboration with a chronic pain team is recommended and should include mental health specialists. Adjunct therapies for pain relief should be incorporated into the care of these children including cognitive behavioral therapy, acupuncture, hypnosis, relaxation, yoga, and massage therapy.

Allogeneic hematopoietic stem cell transplantation has been shown to restore thymidine phosphorylase enzyme function in patients with MNGIE; however, long-term outcomes

and improvement in clinical symptoms in a larger cohort is needed [80]. A role for immunomodulation has been proven effective for patients diagnosed with inflammatory neuropathy or myopathy.

Children with PIPO should be considered for either isolated of multi-visceral transplant for the following reasons: (1) if they suffer a poor quality of life due to recurrent episodes of acute pseudo-obstruction leading to increased morbidity and mortality and (2) if they have developed severe parenteral nutrition associated complications such as intestinal failure associated liver disease, recurrent episodes of central line sepsis, and/or loss of central line access [2]. Based on the report from the United Network for Organ Sharing intestinal transplant database from January 1, 1991 to May 16, 2008, PIPO was the 3rd most common diagnosis (16%) to receive an intestinal transplant with gastroschisis (24%) and short gut syndrome (20%) being more common. The 1-year and 5-year survival rates after intestinal transplant were reported as 75% and 57%, respectively [81].

PIPO is associated with significant morbidity and mortality usually due to the treatments these patients receive. Children with PIPO were found to have less pain free days and increased anxiety and depression compared to healthy children. The increased time and effort to care for them also places a burden on their families [82]. Efforts need to be made to improve their quality of life and reduce the emotional stress on their families. We have made significant strides in better understanding the pathophysiology of PIPO during the neonatal period with advancements in genetic testing. This has allowed for better discussions regarding patient diagnosis and prognosis and may potentially lead to additional treatments in the future.

Compliance with Ethical Standards

Conflict of Interest Manu Sood reports his spouse is an employee and has stock options from AbbVie Pharmaceutical and Abbott, outside the submitted work. Heidi Gamboa declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Rudolph CD, Hyman PE, Altschuler SM, Christensen J, Colletti RB, Cucchiara S, et al. Diagnosis and treatment of chronic intestinal pseudo-obstruction in children: report of consensus workshop. J Pediatr Gastroenterol Nutr. 1997;24:102–12.
2. Thapar N, Saliakellis E, Benninga MA, Borrelli O, Curry J, Faure C, et al. Paediatric intestinal pseudo-obstruction: evidence and consensus-based recommendations from an ESPGHAN-Led Expert Group. J Pediatr Gastroenterol Nutr. 2018;66:991–1019.
3. Dudley HA, Sinclair IS, McLAREN IF, McNAIR TJ, Newsam JE. Intestinal pseudo-obstruction. J R Coll Surg Edinb. 1958;3:206–17.
4. Byrne WJ, Cipel L, Euler AR, Halpin TC, Ament ME. Chronic idiopathic intestinal pseudo-obstruction syndrome in children–clinical characteristics and prognosis. J Pediatr. 1977;90:585–9.
5. Kapur RP, Robertson SP, Hannibal MC, Finn LS, Morgan T, van Kogelenberg M, et al. Diffuse abnormal layering of small intestinal smooth muscle is present in patients with FLNA mutations and x-linked intestinal pseudo-obstruction. Am J Surg Pathol. 2010;34:1528–43.
6. North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Motility Resources. [Internet]. [cited 2019 Sep 13]. https://members.naspghan.org/NASPGHANMembers/Professional_Education/Motility_Resources.aspx. Accessed 20 Aug 2019
7. Di Lorenzo C. Pseudo-obstruction: current approaches. Gastroenterology. 1999;116:980–7.
8. Muto M, Matsufuji H, Tomomasa T, Nakajima A, Kawahara H, Ida S, et al. Pediatric chronic intestinal pseudo-obstruction is a rare, serious, and intractable disease: a report of a nationwide survey in Japan. J Pediatr Surg. 2014;49:1799–803.
9. Pingault V, Girard M, Bondurand N, Dorkins H, Van Maldergem L, Mowat D, et al. SOX10 mutations in chronic intestinal pseudo-obstruction suggest a complex physiopathological mechanism. Hum Genet. 2002;111:198–206.
10. Van Goethem G, Schwartz M, Löfgren A, Dermaut B, Van Broeckhoven C, Vissing J. Novel POLG mutations in progressive external ophthalmoplegia mimicking mitochondrial neurogastrointestinal encephalomyopathy. Eur J Hum Genet EJHG. 2003;11:547–9.
11. Giordano C, Powell H, Leopizzi M, De Curtis M, Travaglini C, Sebastiani M, Gallo P, et al. Fatal congenital myopathy and gastrointestinal pseudo-obstruction due to POLG1 mutations. Neurology. 2009;72:1103–5.
12. Gargiulo A, Auricchio R, Barone MV, Cotugno G, Reardon W, Milla PJ, et al. Filamin A is mutated in X-linked chronic idiopathic intestinal pseudo-obstruction with central nervous system involvement. Am J Hum Genet. 2007;80:751–8.
13. Bott L, Boute O, Mention K, Vinchon M, Boman F, Gottrand F. Congenital idiopathic intestinal pseudo-obstruction and hydrocephalus with stenosis of the aqueduct of sylvius. Am J Med Genet A. 2004;130A:84–7.
14. Milunsky A, Baldwin C, Zhang X, Primack D, Curnow A, Milunsky J. Diagnosis of chronic intestinal pseudo-obstruction and megacystis by sequencing the ACTG2 gene. J Pediatr Gastroenterol Nutr. 2017;65:384–7.
15.•• Dong W, Baldwin C, Choi J, Milunsky JM, Zhang J, Bilguvar K, Lifton RP, et al. Identification of a dominant MYH11 causal variant in chronic intestinal pseudo-obstruction: results of whole-exome sequencing. Clin Genet. 2019;96:473–7. **Through whole exome sequencing, additional gene mutations affecting smooth muscle contractility were identified; this expanded our understanding of intestinal pseudo-obstruction etiologies**.
16. Gauthier J, Ouled Amar Bencheikh B, Hamdan FF, Harrison SM, Baker LA, Couture F, et al. A homozygous loss-of-function variant in MYH11 in a case with megacystis-microcolon-intestinal hypoperistalsis syndrome. Eur J Hum Genet EJHG. 2015;23:1266–8.
17. Wang Q, Zhang J, Wang H, Feng Q, Luo F, Xie J. Compound heterozygous variants in MYH11 underlie autosomal recessive megacystis-microcolon-intestinal hypoperistalsis syndrome in a Chinese family. J Hum Genet. 2019;64:1067–73.

18. Halim D, Brosens E, Muller F, Wangler MF, Beaudet AL, Lupski JR, et al. Loss-of-function variants in MYLK cause recessive megacystis microcolon intestinal hypoperistalsis syndrome. Am J Hum Genet. 2017;101:123–9.
19. Halim D, Wilson MP, Oliver D, Brosens E, Verheij JBGM, Han Y, et al. Loss of LMOD1 impairs smooth muscle cytocontractility and causes megacystis microcolon intestinal hypoperistalsis syndrome in humans and mice. Proc Natl Acad Sci U S A. 2017;114:E2739–47.
20. Moreno CA, Sobreira N, Pugh E, Zhang P, Steel G, Torres FR, et al. Homozygous deletion in MYL9 expands the molecular basis of megacystis-microcolon-intestinal hypoperistalsis syndrome. Eur J Hum Genet EJHG. 2018;26:669–75.
21. Qualia CM, Brown MR, Ryan CK, Rossi TM. Oral mucosal neuromas leading to the diagnosis of multiple endocrine neoplasia type 2B in a child with intestinal pseudo-obstruction. Gastroenterol Hepatol. 2007;3:208–11.
22. Grobmyer SR, Guillem JG, O'Riordain DS, Woodruff JM, Shriver C, Brennan MF. Colonic manifestations of multiple endocrine neoplasia type 2B: report of four cases. Dis Colon Rectum. 1999;42:1216–9.
23. Nishino I, Spinazzola A, Hirano M. Thymidine phosphorylase gene mutations in MNGIE, a human mitochondrial disorder. Science. 1999;283:689–92.
24. Bonora E, Bianco F, Cordeddu L, Bamshad M, Francescatto L, Dowless D, et al. Mutations in RAD21 disrupt regulation of APOB in patients with chronic intestinal pseudo-obstruction. Gastroenterology. 2015;148:771–782.e11.
25.• Chetaille P, Preuss C, Burkhard S, Côté J-M, Houde C, Castilloux J, et al. Mutations in SGOL1 cause a novel cohesinopathy affecting heart and gut rhythm. Nat Genet. 2014;46:1245–9 **This study describes a new syndrome called chronic atrial and intestinal dysrhythmia, an autosomal recessive form of intestinal pseudo-obstruction**.
26. Haas S, Bindl L, Fischer H-P. Autoimmune enteric leiomyositis: a rare cause of chronic intestinal pseudo-obstruction with specific morphological features. Hum Pathol. 2005;36:576–80.
27. Ruuska TH, Karikoski R, Smith VV, Milla PJ. Acquired myopathic intestinal pseudo-obstruction may be due to autoimmune enteric leiomyositis. Gastroenterology. 2002;122:1133–9.
28. Schäppi MG, Smith VV, Milla PJ, Lindley KJ. Eosinophilic myenteric ganglionitis is associated with functional intestinal obstruction. Gut. 2003;52:752–5.
29. Ooms AHAG, Verheij J, Hulst JM, Vlot J, van der Starre C, de Ridder L, et al. Eosinophilic myenteric ganglionitis as a cause of chronic intestinal pseudo-obstruction. Virchows Arch Int J Pathol. 2012;460:123–7.
30. De Giorgio R, Camilleri M. Human enteric neuropathies: morphology and molecular pathology. Neurogastroenterol Motil Off J Eur Gastrointest Motil Soc. 2004;16:515–31.
31. Wildhaber B, Niggli F, Stallmach T, Willi U, Stauffer UG, Sacher P. Intestinal pseudoobstruction as a paraneoplastic syndrome in ganglioneuroblastoma. Eur J Pediatr Surg Off J Austrian Assoc Pediatr Surg Al Z Kinderchir. 2002;12:429–31.
32. Smith VV, Gregson N, Foggensteiner L, Neale G, Milla PJ. Acquired intestinal aganglionosis and circulating autoantibodies without neoplasia or other neural involvement. Gastroenterology. 1997;112:1366–71.
33. Meneghelli UG. Chagasic enteropathy. Rev Soc Bras Med Trop. 2004;37:252–60.
34. Whitehouse FR, Kernohan JW. Myenteric plexus in congenital megacolon; study of 11 cases. Arch Intern Med Chic Ill 1908. 1948;82:75–111.
35. Schäppi MG, Staiano A, Milla PJ, Smith VV, Dias JA, Heuschkel R, et al. A practical guide for the diagnosis of primary enteric nervous system disorders. J Pediatr Gastroenterol Nutr. 2013;57:677–86.
36. Knowles CH, De Giorgio R, Kapur RP, Bruder E, Farrugia G, Geboes K, et al. The London Classification of gastrointestinal neuromuscular pathology: report on behalf of the Gastro 2009 International Working Group. Gut. 2010;59:882–7.
37. Heneyke S, Smith VV, Spitz L, Milla PJ. Chronic intestinal pseudo-obstruction: treatment and long term follow up of 44 patients. Arch Dis Child. 1999;81:21–7.
38. King SK, Sutcliffe JR, Hutson JM. Laparoscopic seromuscular colonic biopsies: a surgeon's experience. J Pediatr Surg. 2005;40:381–4.
39. Knowles CH, Veress B, Tornblom H, Wallace S, Paraskeva P, Darzi A, et al. Safety and diagnostic yield of laparoscopically assisted full-thickness bowel biospy. Neurogastroenterol Motil Off J Eur Gastrointest Motil Soc. 2008;20:774–9.
40. Furness JB. The enteric nervous system. Malden: Blackwell Pub; 2006.
41. Furness JB. The enteric nervous system and neurogastroenterology. Nat Rev Gastroenterol Hepatol. 2012;9:286–94.
42. Faure C, Di Lorenzo C, Thapar N. Pediatric neurogastroenterology: gastrointestinal motility and functional disorders in children [Internet]. New York: Humana Press; 2013 [cited 2019 Sep 13]. Available from:. https://doi.org/10.1007/978-1-60761-709-9.
43. Knowles CH, De Giorgio R, Kapur RP, Bruder E, Farrugia G, Geboes K, et al. Gastrointestinal neuromuscular pathology: guidelines for histological techniques and reporting on behalf of the Gastro 2009 International Working Group. Acta Neuropathol (Berl). 2009;118:271–301.
44. Wood JD. Enteric nervous system (the brain-in-the-gut). San Rafael: Morgan & Claypool; 2011.
45. Fell JM, Smith VV, Milla PJ. Infantile chronic idiopathic intestinal pseudo-obstruction: the role of small intestinal manometry as a diagnostic tool and prognostic indicator. Gut. 1996;39:306–11.
46. Sanders KM, Kito Y, Hwang SJ, Ward SM. Regulation of gastrointestinal smooth muscle function by interstitial cells. Physiol Bethesda Md. 2016;31:316–26.
47. Farrugia G. Interstitial cells of Cajal in health and disease. Neurogastroenterol Motil Off J Eur Gastrointest Motil Soc. 2008;20(Suppl 1):54–63.
48. Feldstein AE, Miller SM, El-Youssef M, Rodeberg D, Lindor NM, Burgart LJ, et al. Chronic intestinal pseudoobstruction associated with altered interstitial cells of cajal networks. J Pediatr Gastroenterol Nutr. 2003;36:492–7.
49. Isozaki K, Hirota S, Miyagawa J, Taniguchi M, Shinomura Y, Matsuzawa Y. Deficiency of c-kit+ cells in patients with a myopathic form of chronic idiopathic intestinal pseudo-obstruction. Am J Gastroenterol. 1997;92:332–4.
50. Kenny SE, Vanderwinden JM, Rintala RJ, Connell MG, Lloyd DA, Vanderhaegen JJ, et al. Delayed maturation of the interstitial cells of Cajal: a new diagnosis for transient neonatal pseudoobstruction. Report of two cases. J Pediatr Surg. 1998;33:94–8.
51. Yamazaki-Nakashimada MA, Rodriguez-Jurado R, Ortega-Salgado A, Gutierrez-Hernández A, García-Pavon-Osorio S, Hernandez-Bautista V. Intestinal pseudoobstruction associated with eosinophilic enteritis as the initial presentation of systemic lupus erythematosus in children. J Pediatr Gastroenterol Nutr. 2009;48:482–6.
52. Yadak R, Breur M, Bugiani M. Gastrointestinal dysmotility in MNGIE: from thymidine phosphorylase enzyme deficiency to altered interstitial cells of Cajal. Orphanet J Rare Dis. 2019;14:33.
53. Mousa H, Hyman PE, Cocjin J, Flores AF, Di Lorenzo C. Long-term outcome of congenital intestinal pseudoobstruction. Dig Dis Sci. 2002;47:2298–305.
54. Faure C, Goulet O, Ategbo S, Breton A, Tounian P, Ginies JL, et al. Chronic intestinal pseudoobstruction syndrome: clinical analysis,

outcome, and prognosis in 105 children. French-Speaking Group of Pediatric Gastroenterology. Dig Dis Sci. 1999;44:953–9.
55. Vargas JH, Sachs P, Ament ME. Chronic intestinal pseudo-obstruction syndrome in pediatrics. Results of a national survey by members of the North American Society of Pediatric Gastroenterology and Nutrition. J Pediatr Gastroenterol Nutr. 1988;7:323–32.
56. Hyman PE, Bursch B, Beck D, DiLorenzo C, Zeltzer LK. Discriminating pediatric condition falsification from chronic intestinal pseudo-obstruction in toddlers. Child Maltreat. 2002;7:132–7.
57. Granata C, Puri P. Megacystis-microcolon-intestinal hypoperistalsis syndrome. J Pediatr Gastroenterol Nutr. 1997;25:12–9.
58. Hyman PE, McDiarmid SV, Napolitano J, Abrams CE, Tomomasa T. Antroduodenal motility in children with chronic intestinal pseudo-obstruction. J Pediatr. 1988;112:899–905.
59. Camilleri M. Jejunal manometry in distal subacute mechanical obstruction: significance of prolonged simultaneous contractions. Gut. 1989;30:468–75.
60. Cucchiara S, Borrelli O, Salvia G, Iula VD, Fecarotta S, Gaudiello G, et al. A normal gastrointestinal motility excludes chronic intestinal pseudoobstruction in children. Dig Dis Sci. 2000;45:258–64.
61. Sigurdsson L, Reyes J, Kocoshis SA, Mazariegos G, Abu-Elmagd KM, Bueno J, et al. Intestinal transplantation in children with chronic intestinal pseudo-obstruction. Gut. 1999;45:570–4.
62. Connor FL, Di Lorenzo C. Chronic intestinal pseudo-obstruction: assessment and management. Gastroenterology. 2006;130:S29–36.
63. Mazziotti MV, Langer JC. Laparoscopic full-thickness intestinal biopsies in children. J Pediatr Gastroenterol Nutr. 2001;33:54–7.
64. Youssef NN, Barksdale E Jr, Griffiths JM, Flores AF, Di Lorenzo C. Management of intractable constipation with antegrade enemas in neurologically intact children. J Pediatr Gastroenterol Nutr. 2002;34:402–5.
65. Di Lorenzo C, Flores AF, Tomomasa T, Hyman PE. Effect of erythromycin on antroduodenal motility in children with chronic functional gastrointestinal symptoms. Dig Dis Sci. 1994;39:1399–404.
66. Di Lorenzo C, Lucanto C, Flores AF, Idries S, Hyman PE. Effect of octreotide on gastrointestinal motility in children with functional gastrointestinal symptoms. J Pediatr Gastroenterol Nutr. 1998;27:508–12.
67. Ambartsumyan L, Flores A, Nurko S, Rodriguez L. Utility of octreotide in advancing enteral feeds in children with chronic intestinal pseudo-obstruction. Paediatr Drugs. 2016;18:387–92.
68. Gomez R, Fernandez S, Aspirot A, Punati J, Skaggs B, Mousa H, et al. Effect of amoxicillin/clavulanate on gastrointestinal motility in children. J Pediatr Gastroenterol Nutr. 2012;54:780–4.
69. Di Lorenzo C, Reddy SN, Villanueva-Meyer J, Mena I, Martin S, Hyman PE. Cisapride in children with chronic intestinal pseudoobstruction. An acute, double-blind, crossover, placebo-controlled trial. Gastroenterology. 1991;101:1564–70.
70. Hyman PE, Di Lorenzo C, McAdams L, Flores AF, Tomomasa T, Garvey TQ. Predicting the clinical response to cisapride in children with chronic intestinal pseudo-obstruction. Am J Gastroenterol. 1993;88:832–6.
71. Giudicessi JR, Ackerman MJ, Camilleri M. Cardiovascular safety of prokinetic agents: a focus on drug-induced arrhythmias. Neurogastroenterol Motil Off J Eur Gastrointest Motil Soc. 2018;30:e13302.
72. Manini ML, Camilleri M, Grothe R, Di Lorenzo C. Application of pyridostigmine in pediatric gastrointestinal motility disorders: a case series. Paediatr Drugs. 2018;20:173–80.
73. Husebye E. Gastrointestinal motility disorders and bacterial overgrowth. J Intern Med. 1995;237:419–27.
74. Barkin JA, Keihanian T, Barkin JS, Antequera CM, Moshiree B. Preferential usage of rifaximin for the treatment of hydrogen-positive smallintestinal bacterial overgrowth. Rev Gastroenterol Peru Organo Of Soc Gastroenterol Peru. 2019;39:111–5.
75. Lu W, Xiao Y, Huang J, Lu L, Tao Y, Yan W, et al. Causes and prognosis of chronic intestinal pseudo-obstruction in 48 subjects: a 10-year retrospective case series. Medicine (Baltimore). 2018;97:e12150.
76. Prapaitrakool S, Hollmann MW, Wartenberg HC, Preckel B, Brugger S. Use of buprenorphine in children with chronic pseudoobstruction syndrome: case series and review of literature. Clin J Pain. 2012;28:722–5.
77. Drossman DA, Tack J, Ford AC, Szigethy E, Törnblom H, Van Oudenhove L. Neuromodulators for functional gastrointestinal disorders (disorders of gut−brain interaction): a Rome Foundation working team report. Gastroenterology. 2018;154:1140–71.
78. Rosner H, Rubin L, Kestenbaum A. Gabapentin adjunctive therapy in neuropathic pain states. Clin J Pain. 1996;12:56–8.
79. Altaf MA, Werlin SL, Sato TT, Rudolph CD, Sood MR. Colonic volvulus in children with intestinal motility disorders. J Pediatr Gastroenterol Nutr. 2009;49:59–62.
80. Hanbali A, Rasheed W, Peedikayil MC, Boholega S, Alzahrani HA. Mitochondrial neurogastrointestinal encephalomyopathy syndrome treated with stem cell transplant: a case series and literature review. Exp Clin Transplant Off J Middle East Soc Organ Transplant. 2018;16:773–8.
81. Lao OB, Healey PJ, Perkins JD, Horslen S, Reyes JD, Goldin AB. Outcomes in children after intestinal transplant. PEDIATRICS. 2010;125:e550–8.
82. Schwankovsky L, Mousa H, Rowhani A, DI Lorenzo C, Hyman PE. Quality of life outcomes in congenital chronic intestinal pseudo-obstruction. Dig Dis Sci. 2002;47:1965–8.