Figure 1

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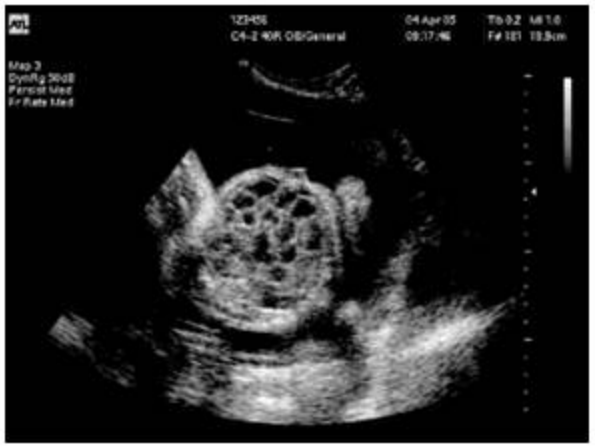

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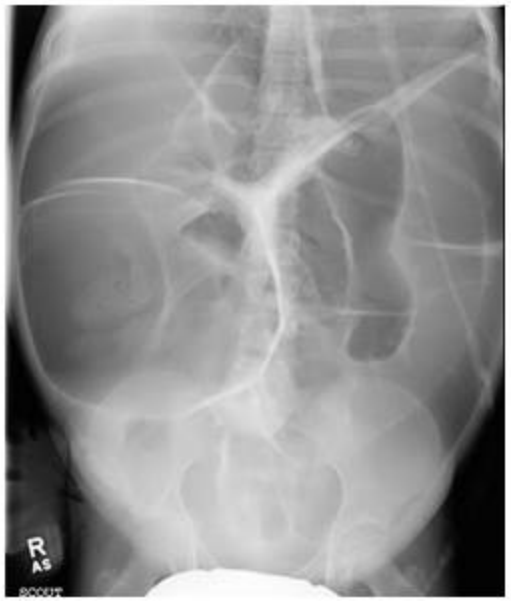

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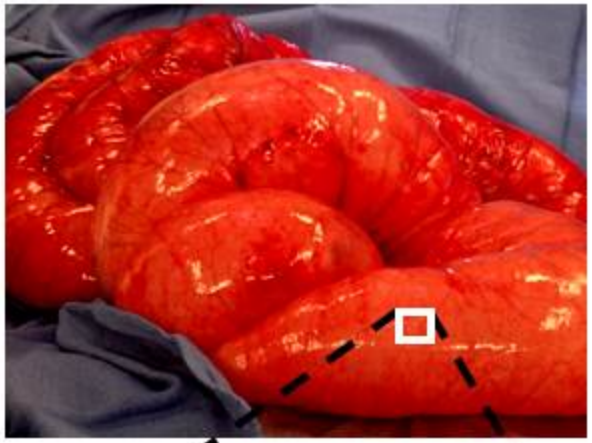

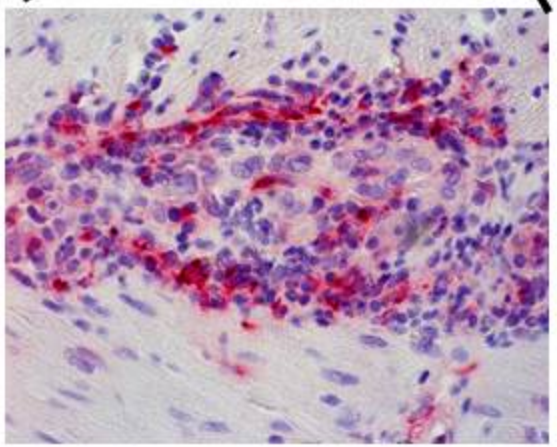

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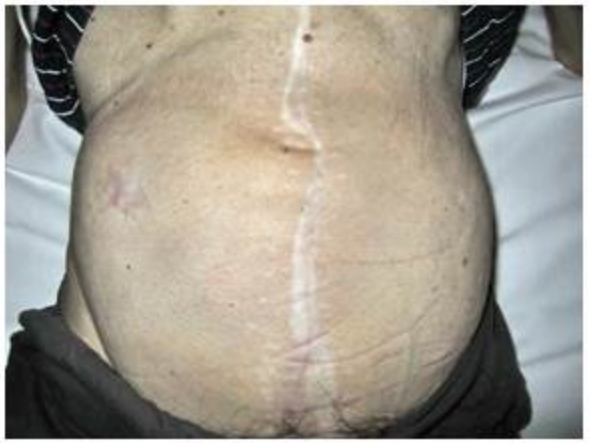

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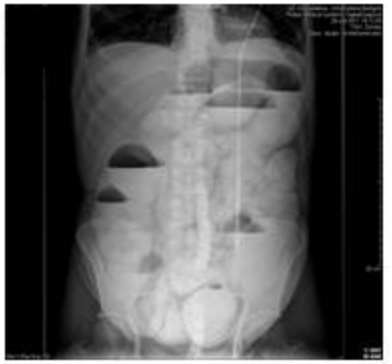

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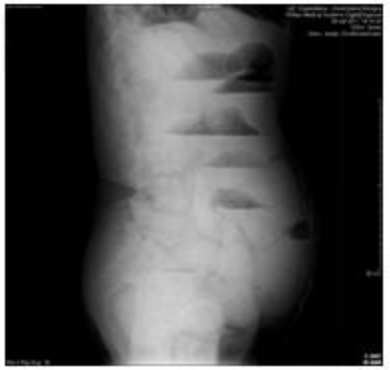
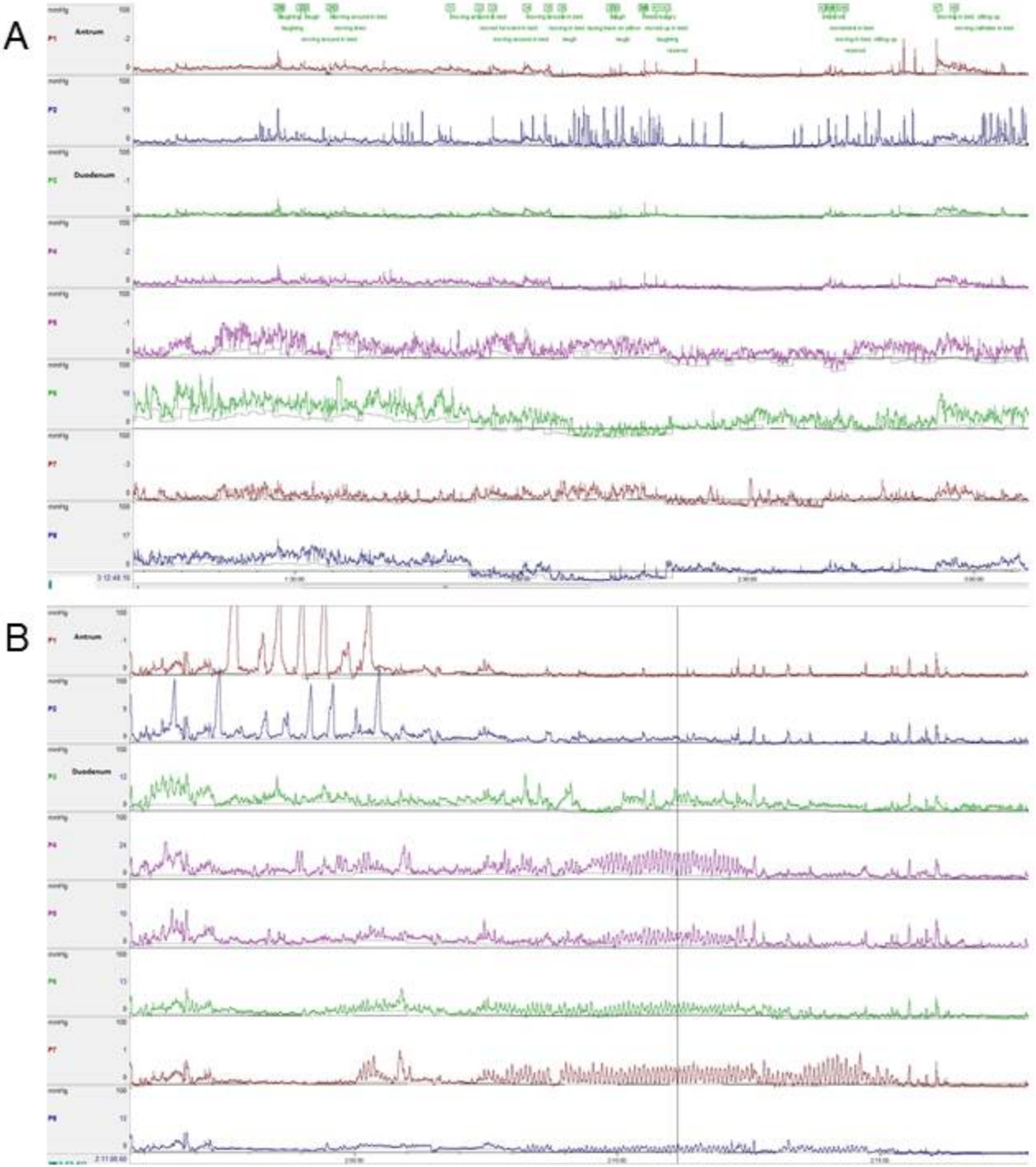


Figure 2



Chronic intestinal pseudo-obstruction in children and adults: diagnosis and therapeutic options

***Running title**:* Chronic intestinal pseudo-obstruction in children and adults

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Abstract

Chronic intestinal pseudo-obstruction (CIPO) represents the most severe form of gastrointestinal dysmotility with debilitating and potentially lethal consequences. Symptoms can be non-specific, and result in this condition being diagnosed incorrectly or too late with consequences for morbidity and even mortality. Thus, the present article aims to provide pediatric and adult gastroenterologists with an up to date review about clinical features, diagnosis and therapeutic options for CIPO. Although pediatric and adult chronic intestinal pseudo-obstruction share many clinical aspects distinctive features can be identified. There is no single diagnostic test or pathognomonic finding of CIPO, thus a stepwise approach including radiology, endoscopy, laboratory, manometry and histopathology should be considered in the diagnostic work-up. Treatment of patients with CIPO is challenging and requires a multidisciplinary effort with participation of appropriately experienced gastroenterologists, pathologists, dieticians, surgeons, psychologists, and other subspecialists based on the presence of comorbidities. Current treatment options invariably involve surgery and specialised nutritional support, especially in children. Medical therapies are mainly aimed to avoid complications such as sepsis or intestinal bacterial overgrowth and, where possible, restore intestinal propulsion. More efficacious therapeutic options are eagerly awaited for such difficult patients.

Key words: Chronic intestinal pseudo-obstruction; clinical manifestations; histopathology; manometry; nutritional therapy.

Key Points

- There is no single diagnostic test or pathognomonic findings for CIPO. The main goals of the diagnostic work up are to exclude bowel mechanical obstruction, to identify underlying diseases and to understand the pathophysiological features.
- Treatment is challenging and requires a multidisciplinary effort.
- Key objectives in the management of patients with CIPO are to avoid unnecessary surgery, restore fluid and electrolyte balance, maintain an adequate caloric intake, promote coordinated intestinal motility and treat bacterial overgrowth.

Introduction

Chronic intestinal pseudo-obstruction (CIPO) is a rare condition characterized by a severe impairment of gastrointestinal (GI) propulsion, which results in symptoms suggestive of partial or complete intestinal obstruction in the absence of any lesion restricting or occluding the intestinal lumen.[1-5] CIPO can involve any segment of the GI tract (although the small bowel and colon are mainly affected) and represents the most severe form of GI dysmotility with potentially lethal consequences.[2,4] Symptoms can be non-specific with CIPO mistaken for other diseases and consequently not diagnosed for long periods of time.[6,7] The chronicity of the severe digestive symptoms, the inability to maintain an adequate nutritional status without specialist support, the suboptimal efficacy of medical treatments, and the limited knowledge of the syndrome by physicians constitute some of the main factors contributing to the poor quality of life and the high morbidity and mortality rate of patients with CIPO.[6-10]

Much like other rare diseases with poorly defined diagnostic criteria, CIPO has a largely unknown prevalence and incidence.[2] One nationwide survey in the U.S. reported that about 100 infants were born with CIPO every year.[11] A more recent nationwide survey in Japan found a prevalence of 3.7 in one million children (1 in 270,000 children younger than 15 years of age) with equal sex incidence.[12] These studies most likely underestimates the true number of new cases per year, as they do not include patients who develop symptoms of CIPO later in life. In another survey of 378 institutions belonging to the Japanese Society of Gastroenterology, CIPO prevalence in adult patients was estimated to be 1.0 and 0.8 cases per 100,000 males and females, respectively. The incidence in the same population was 0.21 and 0.24 cases per 100,000 males and females, respectively.[13]

The purpose of this paper is to provide a broad review of CIPO ranging from pediatric to adult age highlighting selectively the main clinical aspects such as symptoms / signs, diagnosis and therapeutic options in the different age groups. Deliberately, we did not address the putative mechanisms underlying severe gut dysfunction as well as the attendant histopathological features

and the reader is referred to published comprehensive articles on these topics (references 14-57). In Table 1 we have summarized the classification of CIPO in relation to etiopathogenetic factors.

Disease spectrum

CIPO is not a single clinical entity, rather an umbrella term for a range of different diseases leading to severe, end-stage gut motor failure. The most severe cases of the CIPO spectrum are those involving pediatric patients with antenatal (*in utero*) evidence of multivisceral dilation of the hollow viscera (e.g. digestive and urinary systems), often characterized by inability to tolerate enteral feeding and poor prognosis (Figure 1A-B).[8,58-60] This clinical subset represents the most common group of pediatric CIPO patients with diffuse involvement of the GI tract. In these cases, the neuromuscular abnormalities (either genetic or acquired) of the GI tract do not preclude birth, but can be severe enough to generate the onset of symptoms in the early newborn period with reported mortality rates ranging from 10% to 32%.[8,58,59]

More rarely, some cases appear to be acquired after birth being characterized by a variable period of normality followed by progression to intestinal failure with bowel (and often urinary tract) dilatation. In some of the most aggressive forms of acquired CIPO, the histopathological analysis may detect a massive inflammatory (mainly lymphocytic) neuro-muscular infiltrate, reminiscent of the autoimmune pancreatic 'insulitis' underlying insulin-dependent diabetes mellitus of the childhood [25] (Figure 1C-D). These cases of CIPO may respond to an immunosuppressive treatment if the immune-mediated insult has not completely damaged regulatory cells, i.e. enteric nerves, interstitial cells of Cajal (ICC), and smooth muscle.[34-39]

Other cases of pediatric and adult CIPO may occur in patients who experience more insidious mild and nonspecific symptoms (either 'irritable bowel syndrome’ - or 'dyspepsia’ - like) thought not to carry a risk to evolve into severe dysmotility. Nonetheless, some of these patients do progress on to a classic CIPO phenotype over time (Figure 1E-G). We consider them the 'dark-side' of adult CIPO spectrum, i.e. cases in whom a number of factors, including an altered gut microbiota, intestinal

epithelial barrier dysfunction, immune dysregulation and other poorly defined mechanisms may operate, individually or in concert, to impair the neuro-muscular homoestasis.[6] Patients with acute onset of CIPO after abdominal surgery, i.e. mimicking a prolonged postoperative ileus, remain a largely unexplained subset. Other striking examples are those cases occurring after ileal bypass performed to treat morbid obesity, suggesting that surgical manipulation may by itself evoke neuro-myoelectrical abnormalities in predisposed alimentary tracts.[61] A synoptic view of this section is reported in Figure 1.

Clinical findings

CIPO may involve any segment of the GI tract and therefore symptoms can vary from patient to patient based on the location and the extent of the gut segment involved. Also, extra-intestinal manifestations and malnutrition contribute to the clinical features.[5,7,15,62-64] Prenatal signs are only detected in about 20% of cases, whereas 50-70% of patients show clinical signs perinatally (i.e. within the first month of age). Most patients (80%) show clinical manifestations by the first year of age, while the remaining 20% have sporadic onset during the first two decades of life.[8,9,12,58,59] One study indicated that the median age of symptom onset in adults is 17 years.[37]

Both pediatric and adult CIPO shares many clinical aspects, although distinctive features can be identified (Table 2). In any age group, the clinical picture tends to be dominated by abdominal pain and distension (80%), which are particularly severe during acute episodes of pseudo-obstruction.[37] Associated symptoms include nausea and vomiting (75%), constipation (40%), and diarrhea (20%).[6,10,37] Between acute episodes, patients can be minimally symptomatic, or continue to experience severe proximal (anorexia, early satiety, nausea and vomiting) and distal digestive symptoms (constipation, diffuse abdominal pain and / or distension).[6,8] Prevalence and severity of acute episodes that recur at irregular intervals vary from patient to patient. Malnutrition is another significant clinical aspect in any patient with CIPO. This is due to both the limited oral intake, because ingestion of food generally aggravates symptoms, and the intestinal malabsorption related

to the altered gut transit, often associated with dilated bowel loops. In about 30% of CIPO patients small intestinal bacterial overgrowth (SIBO) occurs as a result of intestinal stasis and can cause diarrhea and steatorrhea.[6] Gastroparesis and urinary bladder dysfunction (with or without megacystis and megaureter) are co-morbidities likely sharing similar pathophysiological mechanisms with those underlying CIPO.[2] Also, because of the frustrating ineffectiveness of most therapeutic interventions, patients with CIPO may develop depression or other psychological disorders.[65,66]

In children, there is a higher risk of colonic and small bowel volvulus secondary to severe dysmotility and gut dilatation, congenital adhesions or concurrent malrotation.[8,59,67-69] Urological involvement is commonly identified in patients with familial and congenital forms of CIPO, particularly in the myopathic subgroup, ranging from 36 to 100%.[8,70-73] Findings include urinary retention secondary to bladder atony, hydronephrosis, vesicoureteral reflux, and recurrent urinary tract infections. Megacystis on antenatal ultrasound has been reported in up to 59% of CIPO and this finding may require caesarean delivery.[72,73] The megacystis can be associated with a microcolon, a phenotype referred to as megacystis-microcolon-intestinal-hypoperistalsis syndrome.[4]

Other syndromic form of CIPO are represented by the mitochondrial disorders which in a large adult series account for 19% of all CIPO patients. They are characterized by severe intestinal dysmotility, poor nutritional status and neurologic manifestations, e.g. peripheral neuropathy (with mild to moderate hypoesthesia), proprioceptive ataxia, progressive external ophthalmoplegia with ptosis and hearing loss.[2] GI manifestations are common at presentation and positive family history together with the progressive neurological and nutritional deterioration should alert clinicians to search for mitochondrial disorders.[42,43,74,75]

Secondary systemic forms (i.e. related to underlying conditions) of CIPO are more common in adult patients in whom they occur at much older age.[2] A proximal muscle weakness may indicate the presence of polymyositis and dermatomyositis. Scleroderma is usually associated with skin abnormalities, while the suspicion of a paraneoplastic syndrome should prompt investigations

aimed at uncovering an occult malignancy of the lung, ovary and breast. Finally, forms of CIPO associated with Chagas' disease are common in Latin America and are characterized by combination of dysphagia and cardiomyopathy.[6,7,11,25,26,32,33,76]

Diagnosis

The diagnosis of CIPO is mainly clinical. The diagnostic work up of both children and adults with suspected CIPO has the following goals: 1) rule out mechanical causes of bowel obstruction. This can be achieved by abdominal computed tomography (CT) or plain X-ray; 2) identify any underlying diseases by an accurate laboratory test profile; 3) evaluate the possibility of a drug-induced CIPO-like presentation (e.g. opioids, tricyclic antidepressants, anti-cholinergic agents, anti-Parkinsonian agents, phenothiazines); and 4) understand the pathophysiological features which may direct management or bear prognostic information in selected cases (particularly by performing GI manometry in cases without bowel dilation). Thus, a stepwise approach (as outlined above) is commonly recommended in CIPO and includes radiology, endoscopy, laboratory, manometry and histopathology.

Radiology

A plain radiograph of the abdomen usually identifies the typical signs of intestinal obstruction, i.e. air-fluid levels and dilated bowel loops.[2,12,59] Air-fluid levels are better visualized in the upright position, but lateral views can be useful. In symptomatic patients without these radiographic findings, other conditions (e.g. chronic constipation, irritable bowel syndrome and functional dyspepsia) should be considered.

Fluoroscopic studies should be performed using water-soluble contrast solutions in order to avoid complications related to barium concretions and, at the same time, enhance hydration and transit of intestinal contents. Upper GI series with small bowel follow-through can reveal dilated bowel loops (often involving the stomach and duodenum) with very slow transit, although the latter finding may

not be detectable in some pediatric cases. Intestinal malrotation may be identified in up to a third of children with CIPO.[8] Less common findings include diverticulosis of the small intestine (in 53% of patients with mitochondrial neurogastrointestinal encephalomyopathy, MNGIE, and 42% of scleroderma), and intestinal pneumatosis.[2]

Contrast medium radiologic tests have been recently superseded by dedicated enterography with high-resolution CT[77] or MRI, which more accurately detect mechanical obstruction and intestinal adhesions. Cine-MRI is emerging as a non invasive, radiation-free method for assessing and monitoring GI motility particularly in the pediatric population.[78,79]

Excretory urograms should be performed in patients with urinary symptoms, since neuro-myopathies may affect both the GI tract and urinary system. A chest CT may be necessary to exclude small cell lung cancer in adult patients with suspected paraneoplastic CIPO. Finally, imaging of the brain can identify leukoencephalopathy in CIPO related to MNGIE.[43,74,75]

Endoscopy

Upper GI endoscopy may be useful to exclude a mechanical occlusion of the proximal small intestine as well as to collect duodenal biopsies in cases where celiac disease or eosinophilic gastroenteropathy are suspected.[3] Colonoscopy can be used to rule out mechanical obstruction and decompress the large intestine, although this manoeuvre rarely provides long-term satisfactory results.[80] The wireless motility capsule measures intraluminal pH, temperature, and pressure; however, the role of this technique in the diagnosis of CIPO has not been established yet and its use is thought to be possibly hazardous when a mechanical obstruction has not been definitely ruled out.[81]

Laboratory tests

Laboratory exams are aimed to uncover secondary causes of CIPO. Blood tests for diabetes mellitus (i.e. hemoglobin A1C and / or postprandial blood glucose concentration), celiac disease (anti-tissue

transglutaminase IgA and anti-deamidated gliadin peptides IgG), connective tissue and skeletal muscle disorders (anti-nuclear antibody, anti-double-stranded DNA and SCL-70, creatine phosphokinase, aldolase), and hypothyroidism should be performed. Other tests include serology for Chagas' disease, urinary catecholamines for pheochromocytoma, and enteric neuronal autoantibodies (anti-Hu or type 1 anti-neuronal nuclear antibodies) in patients with suspected paraneoplastic syndrome. Urinary porphyrins should be assayed in patients with severe, otherwise unexplained abdominal pain. A complete blood cell count, electrolytes, albumin, liver enzymes, vitamin B12, fasting cortisol, inflammatory indexes (C-reactive protein and erythrocyte sedimentation rate) are useful in all cases.[66] Patients receiving parenteral nutrition (PN) should be carefully monitored with particular attention to fluid, electrolytes and circulating levels of trace elements. In patients with symptoms and signs suggestive of an underlying mitochondrial disorder, serum lactate and thymidine phosphorylase activities should be performed. If thymidine phosphorylase activity is markedly reduced / absent and nucleosides are increased, then thymidine phosphorylase (*TYMP*) (in MNGIE), and polymerase DNA-gamma (*POLG*) (in sensory ataxic neuropathy dysarthria and ophthalmoparesis) gene mutations should be tested.[74,75]

Manometry

Intestinal manometry can be useful to define the pathophysiological (neuro-muscular) mechanisms involved in CIPO (e.g. neuropathy or myopathy), although it has a low diagnostic specificity and in most pediatric and adult patients does not influence treatment. Nonetheless, intestinal manometry can differentiate mechanical from functional forms of sub-occlusion, provided that the organic cause is at an early stage.[6,7,10,62,63,82-86] The presence of postprandial, prolonged, high pressure, non-propagated contractions is a pattern suggestive of a recently occurred mechanical obstruction.[5,7,10,11] A neuropathy is characterized by contractions showing a normal amplitude, although with uncoordinated pattern[5,7,10,11] (Figure 2), whereas coordinated contractions with a reduced amplitude are indicative of an enteric myopathy. However, a careful interpretation is mandatory since low-

amplitude contractions could be secondary to the inability of the manometric catheter to register non-occlusive contractions when bowel loops are dilatated.[2] Antroduodenal manometry has been applied extensively in children in order to assess prognosis, response to treatment and tolerance to oral feeding.[82-84] In children with chronic symptoms suggestive of CIPO, a normal manometry essentially excludes CIPO and should lead to the consideration of emotional or factitious disorders (e.g. Munchausen syndrome by proxy).[85,86] Amiot et al. have identified abnormal esophageal manometry in 73% (51% with severe ineffective dysmotility) adult CIPO cases.[87] Similar findings have been also documented in paediatric cases of CIPO.[59] Notably, only esophageal motor disorders had a significantly negative predictive value in terms of survival, home PN requirement, and inability to maintain sufficient oral feeding, suggesting the presence of a more generalized disease.[87] Also, esophageal manometry may have diagnostic value in CIPO associated with scleroderma. Anorectal manometry is indicated when the clinical picture is characterized by intractable constipation and marked colonic dilatation, suggestive of Hirschsprung's disease.[2] A careful manometric assessment of the entire GI tract, including the colon, has been deemed helpful in helping to plan for an isolated or a multivisceral transplantation in the most severe forms of pediatric CIPO.[11]

Histopathology

Collection of gut full-thickness biopsies is aimed at providing clinicians with a histopathological correlate which may unravel abnormalities related to: *a*) extrinsic and/or intrinsic neurons controlling gut functions; *b*) the ICC networks; and *c*) enteric smooth muscle cells. Changes affecting these cellular systems are tightly linked to the pathophysiology of CIPO and may have prognostic and sometimes therapeutic implications. [88,89] Minimally invasive procedures, e.g. laparoscopic surgery or - very recently - endoscopic approaches (for example natural-orifice translumenal endoscopic surgery), have shown a high diagnostic yield and safety.[90] In addition, guidelines proposed by the Gastro 2009 International Working Group have helped to find consensus

about technical aspects (including tissue collection and processing) and histopathological reporting of results in a variety of gut neuro-muscular disorders, including CIPO.[24,44]

In the absence of clinical guidelines, we suggest that ideal CIPO patients who should be referred to laparoscopic surgery for full-thickness biopsies fall into these two major categories: 1) idiopathic cases characterized by an acute onset likely of post-infectious origin; 2) patients with progressive, rapidly evolving forms of CIPO who are not under treatment with opioids and do not respond to any therapeutic options. In contrast, CIPO patients with severe pain, not uncommonly treated with opioids, should not undergo intestinal biopsy. In those cases it is advisable to taper down opioids and change with other non-opioidergic analgesic compounds. This measure is directed to avoid useless and often misleading histopathological analysis. In CIPO cases with a clear origin (i.e. secondary forms of CIPO), tissue sampling may be less clinically meaningful as many systemic diseases are known to affect the gut neuro-muscular layer.

Natural history

A severe clinical course can be expected for both pediatric and adult patients with CIPO when an underlying treatable disease is not identified.[6,62-64,71] In a single-centre study of 59 adult patients with idiopathic CIPO followed up for a long time (13 years), it was demonstrated that the average time between the first sub-occlusive episode and the diagnosis of CIPO was 8 years, with 88% of patients undergoing an average of 3 unnecessary surgical procedures.[6] Similar rates of questionable surgery are seen in the pediatric setting.[59] The digestive symptoms worsened over time with abdominal pain becoming intractable or responsive only to major analgesics (e.g. opioids - always used parsimoniously and with extreme caution in our own experience) in approximately 25% of cases.[6] Most patients had oral feeding restrictions, while 30%-50% of patients needed long term PN.[6,62,63] A study by Amiot et al., which examined all patients with CIPO on PN at home, revealed that the lowest mortality was associated with the ability to restore oral feeding and with the

presence of symptoms before 20 years of age, while an increased mortality was associated with the presence of scleroderma.[62]

Manometric parameters, such as inadequate or absent motor response to meals, absence of migrating motor complex (MMC) during fasting, and generalized hypomotility have been shown to be predictive of poor outcome in patients with CIPO.[62,84] Finally, detection of esophageal dysmotility in CIPO seems to have negative prognostic implications in terms of mortality and need for home PN.[87] In children with CIPO, a myopathic etiology, coexisting urinary involvement, and concurrent intestinal malrotation are poor prognostic factors.[8] In both adults and children, the risk of death is increased by the absence of a specialist team and in the early phases after the diagnosis of intestinal failure has been established.[91]

Therapy

Treatment of patients with CIPO is challenging and requires a multidisciplinary effort. The management of both children and adults with CIPO should be directed to avoid unnecessary surgery, restore fluid and electrolyte balance, maintain an adequate caloric intake, promote coordinated intestinal motility, and treat complications e.g. sepsis, SIBO and associated symptoms. In general, current therapeutic approaches are not very effective; however, recent advancement in nutritional, pharmacological and surgical treatment has helped to improve the management of patients with CIPO.[2,4,5,7]

Nutritional support

Patients with CIPO are often malnourished, due to malabsorption and insufficient food intake. Patients with sufficient intestinal absorption capacity should be encouraged to take small, frequent meals (5-6 / day), with an emphasis on liquid calories and protein intake, while avoiding high-fat and high-residue (fiber containing) foods. Carbohydrate containing foods, rich in lactose and fructose, may worsen abdominal bloating and discomfort.[3] Vitamin levels, i.e. A, D, E and K as

well as B12 and folic acid, should be supplemented when needed. In cases of inadequate oral intake, enteral nutrition with standard non-elemental formula may be considered. In children, extensively hydrolysed and elemental formulas are often empirically used to facilitate intestinal transit and absorption.[4,5,92] Before a permanent feeding tube is placed, a trial with a nasogastric or nasojejunal feeding tube should be attempted using an enteral formula at a rate sufficient to provide an adequate caloric support.[91,93,94] When delayed gastric emptying is present, bypassing the stomach and directing the feeding into the small intestine is generally preferred. Jejunal feeding tubes were tolerated in all patients with manometrically detectable MMC *vs.* 33% of those without. Enteral nutrition should be started with a slow infusion given continuously or, preferably, in a cyclical manner (during the night).[3]

In the most severe cases, PN is necessary to maintain nutritional support and an adequate level of hydration.[93-94] If patients are exclusively dependent on PN, they should receive approximately 25 kcal / kg / day, and lipids should approximately supply 30% of total parenteral calories with 1.0-1.5 g / kg / day of proteins and dextrose covering the remaining caloric amount.[93-94] Complications of PN, including liver failure, pancreatitis, glomerulonephritis, thrombosis and sepsis, are frequent causes of morbidity and mortality in any form of pediatric and adult CIPO.[91,93] Individualized PN formulations with minimal amount of intravenous lipids can help reducing metabolic complications. A long-term PN does not seem to be associated with a significant increase in morbidity and mortality in CIPO.[93] A retrospective analysis of 51 adult patients receiving PN for an average of 8.3 years showed 180 episodes of catheter-related sepsis, 9 of acute pancreatitis, 5 encephalopathy, and 4 patients progressing to cirrhosis.[62] Oral intake was a major independent factor associated with better survival; thus, patients receiving PN should be allowed and encouraged to maximize oral intake as tolerated.[93,96]

Pharmacologic therapy

The main aim of pharmacological treatment in patients with CIPO is to promote GI propulsive activity, thereby improving oral feeding, decreasing symptom severity, and minimizing SIBO.[2-4]

The efficacy and main features related to various drugs, such as erythromycin, metoclopramide, domperidone, somatostatin analogues (octreotide and lanreotide), cholinesterases inhibitors (neostigmine and pyridostigmine), serotoninergic agents (such as 5-hydroxytryptamine receptor 4 - 5-HT_4 - agonists, e.g. prucalopride), prostaglandins and gonadotropin-releasing hormone analogues (leuprolide), have been reported in a number of pediatric and adult CIPO studies (Table 3).[97-113]

Erythromycin is a macrolide antibiotic mimicking the prokinetic hormone motilin that induces phase III of the MMC. It has shown to be effective (at a dose of 1.5-2 g/day in adults or 3-5 mg/kg/dose in children) in accelerating gastric emptying and improving symptoms of CIPO in case reports.[4,97] Metoclopramide and domperidone are two orthopramides which exert their prokinetic effects via type 2 dopamine receptor antagonism and increasing acetylcholine release from myenteric neurons. Although widely used in patients with functional gut disorders,[7] there are no clinical data regarding their use in CIPO. In addition, metoclopramide has a boxed warning by the Food and Drug Administration due to the risk of tardive dyskinesia.[98] Octreotide, a long-acting analogue of somatostatin, is known to evoke phase III of the MMC in the small intestine of patients with scleroderma-related CIPO.[99] Subcutaneous octreotide at a dose of 50 mcg/day resulted in a significant beneficial effect by relieving bacterial overgrowth in those patients.[99] Further studies confirmed its efficacy showing reduction of nausea, vomiting, bloating, and abdominal pain, in a subset of idiopathic CIPO.[100] The acetylcholinesterase inhibitor neostigmine has proven efficacy in colonic decompression in adult and pediatric acute colonic pseudo-obstruction.[101] Repeated use was successful in an adult patient with colonic pseudo-obstruction, although chronic use in children with CIPO has not been reported.[102] The longer acting pyridostigmine has also been used with success in adult patients with CIPO.[103] Among the newly discovered highly selective 5-HT_4 receptor agonists, prucalopride has shown high bioavailability and lack of major interactions with other drugs as it is not metabolized by the cytochrome P3A4.[104] Prucalopride exerts a significant enterokinetic effects

[105] and a recent randomized, controlled trial on CIPO patients (3 patients had visceral myopathy; 1 visceral neuropathy; all treated with 2-4 mg once daily and followed for 48 weeks), showed beneficial symptomatic effects and lower use of analgesic drugs.[106] Although the sample size was very small, the results of this study lend support to future multicenter controlled trials.

SIBO is known to cause mucosal inflammation, which further impairs GI motility thereby contributing to nausea, bloating and abdominal distension.[2,107-112] Various antibiotic regimens have been recommended.[110] The treatment of choice usually involves the use of non-absorbable antibiotics, such as rifaximin.[111] Nonetheless, most clinicians use 1- to 2-week rotation of broad-spectrum antibiotics such as amoxicillin and clavulanic acid, gentamicin, and metronidazole, often combined with an antifungal compound (e.g., nystatin or fluconazole) followed by antibiotic-free periods.[2] Notably, amoxicillin-clavulanate has been shown to combine antibiotic and enterokinetic properties in children.[112]

Non-narcotic pain modulators, such as tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors, should be used with caution in CIPO patients due to their significant side effects (i.e. constipation and / or drowsiness). Starting with low doses followed by gradual increase is advisable to optimise the beneficial / side effect ratio. Gabapenentinoids (gabapentin and pregabalin) as well as peripherally acting μ-opioid receptor antagonists (PAMORAs) may represent promising alternatives to antidepressants; however studies in patients with CIPO are lacking. If visceral pain is untreatable, an extremely careful and cautionary use of opiates may be attempted. In children with CIPO and significant abdominal pain, transdermal buprenorphine (5 mcg / h), a μ-partial agonist and κ- and δ-opioid receptor antagonist, has shown adequate pain relief in 3 out of 4 patients.[113]

In CIPO characterized by histopathological signs of marked inflammation / immune response within myenteric ganglia or throughout the neuromuscular tract, immunosuppressive drugs (e.g., steroids and azathioprine), might be an effective therapeutic options.[34,35,38] Treatment of secondary forms of CIPO is mainly directed toward the underlying diseases (e.g., scleroderma, paraneoplastic

syndrome, endocrine related disorders and many others) in addition to gut-directed therapy such as antibiotics, prokinetics and laxatives.

Endoscopic and Surgical therapy

Decompression of distended GI segments via intermittent nasogastric suction, rectal tubes or endoscopy in both adults and children is an important therapeutic target.[2,3,114] In some cases a "venting" enterostomy,[115] typically placed endoscopically in the intestine, may be necessary. Recently, repetitive colonoscopic decompression has been successfully used as a bridge therapy before surgery in a pregnant woman with CIPO.[116] In adult patients needing multiple endoscopic decompression, percutaneous endoscopic colostomy has been recently proposed as a feasible therapeutic option since it leads to durable symptom relief without risk of surgical intervention.[117]

The role of surgery in CIPO has been debated over the years. Although its use may be indicated as a tool to collect gut biopsy specimens for histopathology, the need for surgical therapy is sometimes required in emergency situations (massive bowel distension and perforation / ischemia). In a retrospective study on 63 adult patients there was an overall postoperative mortality rate of 7.9%, while CIPO-related re-operation rate was 66% at 5 years.[118,119] In children palliative procedures such as feeding / venting gastrostomies and jejunostomies are mainly used to relieve symptoms in half of the patients. [9,120,121] It is important to keep in mind that when a surgical procedure is performed in a CIPO patient, full-thickness biopsies should be obtained and processed in dedicated centres.

Transplantation

Intestinal transplantation (isolated or multivisceral) is thought a reasonable therapeutic alternative for patients with CIPO who experience serious complications of PN (e.g. liver failure or recurrent sepsis arising from a central venous catheter). Other indications to transplantation are the inability to obtain venous access for PN and a poor quality of life while on PN.[95] Patients with CIPO account

for approximately 9% of the total intestinal transplants in both adults and children.[122-125] Patients with CIPO should be evaluated for urological abnormalities and antibiotic prophylaxis for urinary tract infections is often required following transplant in these patients.

The development of new immunosuppressive agents such as tacrolimus and novel induction agents (basiliximab, alemtuzumab, daclizumab and anti-lymphocyte globulins) have been associated with an increased overall survival rate and reduced graft rejection rate.[126,127] Complications include acute rejection, opportunistic infections, e.g. cytomegalovirus and Epstein-Barr virus, and surgical morbidity including wound infections, stoma-related complications, graft ischemia, intestinal perforations, delayed gastric emptying, intestinal obstruction and biliary tract dilatation.

In the presence of gastric involvement, modified multivisceral transplantation (stomach-duodenum-pancreas plus small bowel) should be performed, even though some reports described the possibility to overcome this issue by transplanting the bowel and modifying surgically the stomach in order to facilitate gastric emptying.[127] In children, PN-related liver failure represents an indication for combined transplant (liver and bowel), but a full multivisceral transplantation (modified multivisceral graft plus liver) is rarely required. While isolated small bowel and liver-bowel transplantation have reasonable long term-results, multivisceral transplant should be performed only in very selected cases and in experienced centers. A study by the University of Miami including 98 adult patients undergoing multivisceral transplantation showed patient and graft survival rates of 49% and 47%, respectively, at a 5-year follow up.[125] Italian experiences in adult patients with CIPO showed that isolated intestinal transplantation performed with different surgical approaches (in order to reduce the delayed post-surgical gastric emptying) had patient survival rates of 70% at 5 years.[127] These results are comparable to those of intestinal transplant in patients with underlying diseases distinct from CIPO.[128-129] The same data have been reported by the United Network for Organ Sharing in children transplanted for CIPO with a 5-year survival rate of 57%, which is comparable to the overall survival rates for intestinal transplant.[123] These data were also recently confirmed by an Italian study with a reported survival rate for recipient of intestinal grafts, in any

combination, of 75% at 2-year follow up.[130] Notably, the catch-up growth seen in children following liver transplantation has not been demonstrated in children with intestinal transplantation. This is probably related to the severity of the illness at the time of presentation and the use of intense immunosuppression, including long-term corticosteroids.[122]

Concerning extra-digestive organ transplant, the allogeneic haematopoietic stem cell transplantation (AHSCT) can be used to restore thymidine phosphorylase enzyme function which is the key biochemical deficit in patients with MNGIE. However, so far the results of AHSCT at a 10-year follow up show that only about 30% of transplanted MNGIE patients are alive. This finding prompted research to focus on alternative tissue source of thymidine phosphorylase.[131] Based on recent data displaying that the liver has high thymidine phosphorylase expression, we have recently transplanted a MNGIE patient with promising results.[132]

Conclusions

CIPO is a rare and severe condition resulting in a marked impairment of GI motility with the appearance of a mechanical obstruction, without any detectable mechanical cause. Although still a challenge for most clinicians and surgeons, the future of CIPO may be more promising than one would expect thanks to a number of important achievements. First, less invasive diagnostic tests, such as cine-MRI and even endoscopic approaches for full thickness biopsy sampling are novel tools that are expected to facilitate identification and investigation of CIPO patients. Second, the classification of enteric neuro-ICC-myopathies and guidelines for tissue processing and analysis represents a hallmark for tissues analysis aimed to identify novel targeted therapeutic options. Third, many prokinetic agents are in the pharma pipeline ready to be tested in clinical trials. Fourth, intestinal transplantation is improving as confirmed by recently published studies. In conclusion, the advancements so far obtained and those expected in the next years are likely to shed light on CIPO patients, their management and related therapeutic options.

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The authors declare no competing interests.

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All authors contributed equally to all aspects of this article.

Literature evaluation for the present review:

A search was performed using Medline and Premedline from 1950 to June 2016. MeSH and free-text terms were chosen to negate problems of syntax, with six iterations of chronic intestinal pseudo-obstruction and children, diagnosis, therapy, comorbidities, natural history, incorporated. Search terms were 'chronic intestinal pseudo-obstruction and children, diagnosis, therapy, comorbidities, natural history' OR 'chronic intestinal pseudo-obstruction/diagnosis' OR 'chronic intestinal pseudo-obstruction/natural history' OR 'chronic intestinal pseudo-obstruction/drug therapy' OR 'chronic intestinal pseudo-obstruction/nutritional therapy' OR 'chronic intestinal pseudo-obstruction/surgical therapy' OR 'chronic intestinal pseudo-obstruction/intestinal transplantation'. Only English language papers were included; the bibliographies of relevant papers were searched, including for earlier papers.

References

1. Stanghellini V, Corinaldesi R, Barbara L. Pseudo-obstruction syndromes. Baillieres Clin Gastroenterol 1988;2:225-54.
2. De Giorgio R, Cogliandro RF, Barbara G, Corinaldesi R, Stanghellini V. Chronic intestinal pseudo-obstruction: clinical features, diagnosis, and therapy. Gastroenterol Clin North Am 2011;40:787-807.
3. Gabbard SL, Lacy BE. Chronic intestinal pseudo-obstruction. Nutr Clin Pract 2013;28:307-316.
4. Yeung AK, Di Lorenzo C. Primary gastrointestinal motility disorders in childhood. Minerva Pediatr 2012;64:567-584.
5. Connor FL, Di Lorenzo C. Chronic intestinal pseudo-obstruction: assessment and management. Gastroenterology 2006;130:29-36.
6. Stanghellini V, Cogliandro RF, De Giorgio R *et al*. Natural history of chronic idiopathic intestinal pseudo-obstruction in adults: a single center study. Clin Gastroenterol Hepatol 2005;3:449-458.
7. Stanghellini V, Cogliandro RF, De Giorgio R *et al.* Chronic intestinal pseudo-obstruction: manifestations, natural history and management. Neurogastroenterol Motil 2007;19:440-452.
8. 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;81:21-27.
9. 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;7:323-332.
10. Stanghellini V, Camilleri M, Malagelada JR. Chronic idiopathic intestinal pseudoobstruction: clinical and intestinal manometric findings. Gut 1987;28:5-12.

11. Di Lorenzo C. Pseudo-obstruction: current approaches. Gastroenterology 1999;116:980-987.
12. Muto, M Matsufuji H, Tomomasa T *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.
13. Lida H, Ohkudo H, Inamori M, Nakajiama A, Sato H. Epidemiology and clinical experience on chronic intestinal pseudo-obstruction in Japan: a nationwide epidemiologic survey. J Epidemiol 2013;23:288-294.
14. Di Nardo G, Blandizzi C, Volta U *et al*. Review article: molecular, pathological and therapeutic features of human enteric neuropathies. Aliment Pharmacol Ther 2008;28:25-42.
15. De Giorgio R, Sarnelli G, Corinaldesi R, Stanghellini V. Advance in our understanding of the pathology of chronic intestinal pseudo-obstruction. Gut 2004;53:1549-1552.
16. Badari A, Farolino D, Nasser E, Mehboob S, Crossland D. A novel approach to paraneoplastic intestinal pseudo-obstruction. Support Care Cancer 2012;20:425-428.
17. Sodhi N, Camilleri M, Camoriano JK *et al*. Autonomic function and motility in intestinal pseudo-obstruction caused by paraneoplastic syndrome. Dig Dis Sci 1989;34:1937-1942.
18. De Giorgio R, Ricciardiello L, Naponelli V *et al*. Chronic intestinal pseudo-obstruction related to viral infections. Transplant Proc 2010;42:9–14.
19. Debinsky HS, Kamm MA, Talbot IC *et al*. DNA viruses in the pathogenesis of sporadic chronic idiopathic intestinal pseudo-obstruction. Gut 1997;41:100-106.
20. Besnard M, Faure C, Fromont-Hankard G *et al*. Intestinal pseudoobstruction and acute pandysautonomia associated with Epstein-Barr virus infection. Am J Gastroenterol 2000;95:280-283.
21. Khairullah S, Jasmin R, Yahya F et al. Chronic intestinal pseudo-obstruction: a rare first manifestation of Systemic lupus erythematosus. Lupus 2013;22:957-960.

22. Stanghellini V, Corinaldesi R, Ghidini C *et al*. Reversibility of gastrointestinal motor abnormalities in chronic intestinal pseudo-obstruction. Hepatogastroenterology 1992;39:34–38.
23. De Giorgio R, Camilleri M. Human enteric neuropathies: morphology and molecular pathology. Neurogastroenterol Motil;16:515-531.
24. Knowles CH, De Giorgio R, Kapur RP *et al*. The London Classification of gastrointestinal neuromuscular pathology: report on behalf of the Gastro 2009 International Working Group. Gut 2010;59: 882-887.
25. De Giorgio R, Guerrini S, Barbara G *et al*. Inflammatory neuropathies of the enteric nervous system. Gastroenterology 2004;126:1872-1883.
26. De Giorgio R, Barbara G, Stanghellini V *et al*. Idiopathic myenteric ganglionitis underlying intractable vomiting in a young adult. Eur J Gastroenterol Hepatol 2000;12:613-6.
27. Smith VV, Gregson N, Foggensteiner L, Neale G, Milla PJ. Acquired intestinal aganglionosis and circulating autoantibodies without neoplasia or other neural involvement. Gastroenterology 1997;112:1366-1371.
28. De Giorgio R, Barbara G, Stanghellini V *et al*. Clinical and morphofunctional features of idiopathic myenteric ganglionitis underlying severe intestinal motor dysfunction: a study of three cases. Am J Gastroenterol 2002;97:2454-2459.
29. Knowles CH, Silk DB, Darzi A *et al*. Deranged smooth muscle alpha-actin as a biomarker of intestinal pseudo-obstruction: a controlled multinational case series. Gut 2004;53:1583-9.
30. Lindberg G, Törnblom H, Iwarzon M *et al*. Full-thickness biopsy findings in chronic intestinal pseudo-obstruction and enteric dysmotility. Gut 2009;58:1084-1090.
31. Veress B Nyberg B, Törnblom H, Lindberg G. Intestinal lymphocytic epithelioganglionitis: a unique combination of inflammation in bowel dysmotility: a histopathological and immunohistochemical analysis of 28 cases. Histopathology 2009;54:539-549.

32. De Giorgio R, Bovara M, Barbara G *et al*. Anti-HuD-induced neuronal apoptosis underlying paraneoplastic gut dysmotility. Gastroenterology 2003;25:70-79.

33. Hubball A, Martin JE, Lang B, De Giorgio R, Knowles CH. The role of humoral autoimmunity in gastrointestinal neuromuscular diseases. Prog Neurobiol 2009;87:10-20.

34. Schäppi MG, Smith VV, Milla PJ, Lindley KJ. Eosinophilic myenteric ganglionitis is associated with functional intestinal obstruction. Gut 2003;52:752–755.

35. Ooms AH, VerheiJ J, Hulst JM *et al*. Eosinophilic myenteric ganglionitis as a cause of chronic intestinal pseudo-obstruction. Virchows Arch 2012;460:123-127.

36. Accarino A. Mast cell neuromuscular involvement in patients with severe gastrointestinal dysmotility (SGID). Gut 2007;56(Suppl III):A18.

37. Mann SD, Debinski HS, Kamm MA. Clinical characteristics of chronic idiopathic intestinal pseudo-obstruction in adults. Gut 1997;41:675-681.

38. Oton E, Moreira V, Redondo C *et al*. Chronic intestinal pseudoobstruction due to lymphocytic leiomyositis: is there a place for immunomodulatory therapy? Gut 2005;54:1343-1344.

39. Dewit S, de Hertogh G, Geboes K, Tack J *et al*. Chronic intestinal pseudo-obstruction caused by an intestinal inflammatory myopathy: case report and review of the literature. Neurogastroenterol Motil 2008;20:343-348.

40. Smith JA, Hauser SC, Madara JL. Hollow visceral myopathy: a light- and electronmicroscopic study. Am J Surg Pathol 1982;6:269-675.

41. Schuffler MD. Chronic intestinal pseudo-obstruction syndromes. Med Clin North Am 1981;65:1331-1358.

42. Bardosi A, Creutzfeldt W, Di Mauro S, *et al*. Myo-, neuro-, gastrointestinal encephalopathy (MNGIE syndrome) due to partial deficiency of cytochrome-c-oxidase. A new mitochondrial multisystem disorder. Acta Neuropathol 1987;74:248-258.

43. Giordano C, Sebastiani M, De Giorgio R *et al*. Gastrointestinal dysmotility in mitochondrial neurogastrointestinal encephalomyopathy is caused by mitochondrial DNA depletion. Am J Pathol 2008;173: 1120-1128.
44. Knowles CH, De Giorgio R, Kapur RP *et al*. Gastrointestinal neuromuscular pathology: guidelines for histological techniques and reporting on behalf of the Gastro 2009 International Working Group. Acta Neuropathol 2009;118:271-301.
45. Farrugia G. Interstitial cells of Cajal in health and disease. Neurogastroenterol Motil 2008;20 (Suppl 1):54-63.
46. Kenny SE, Vanderwinden JM, Rintala RJ *et al*. Delayed maturation of the interstitial cells of Cajal: a new diagnosis for transient neonatal pseudo-obstruction: report of two cases. J Ped Surg 1998;33:94-98.
47. Struijs MC Diamond IR, Pencharz PB *et al*. Absence of the interstitial cells of Cajal in a child with chronic pseudo-obstruction. J Pediatr Surg 2008;43:E25-29.
48. De Giorgio R, Seri M, Cogliandro R *et al*. Analysis of candidate genes for intrinsic neuropathy in a family with chronic idiopathic intestinal pseudo-obstruction. Clin Gen 2001;59:131-133.
49. Pingault V, Guiochon-Mantel A, Bondurand N *et al*. Peripheral neuropathy with hypomyelination, chronic intestinal pseudo-obstruction and deafness: a developmental "neural crest syndrome" related to a SOX10 mutation. Ann Neurol 2000;48:671-676.
50. Pingault V, Girard M, Bondurand N *et al*. SOX10 mutations in chronic intestinal pseudo-obstruction suggest a complex physiopathological mechanism. Hum Genet 2002;111:198-206.
51. Mungan Z, Akyüz F, Bugra Z *et al*. Familial visceral myopathy with pseudo-obstruction, megaduodenum, Barrett's esophagus, and cardiac abnormalities. Am J Gastroenterol 2003;98:2556-2560.

52. Deglincerti A, De Giorgio R, Cefle K *et al*. A novel locus for syndromic chronic idiopathic intestinal pseudo-obstruction maps to chromosome 8q23-q24. Eur J Hum Genet 2007;15:889-897.
53. Nishino I, Spinazzola A, Hirano M. Thymidine phosphorylase gene mutations in MNGIE, a human mitochondrial disorder. Science 1999;283:689-692.
54. Van Goethem G, Schwartz M, Löfgren A *et al*. Novel POLG mutations in progressive external ophthalmoplegia mimicking mitochondrial neurogastrointestinal encephalomyopathy. Eur J Hum Genet 2003;11:547-549.
55. Gargiulo A, Auricchio R, Barone MV *et al*. Filamin A is mutated in X-linked chronic idiopathic intestinal pseudo-obstruction with central nervous system involvement. Am J Hum Genet 2007;80:751-758.
56. Clayton-Smith J, Walters S, Hobson E *et al*. Xq28 duplication presenting with intestinal and bladder dysfunction and a distinctive facial appearance. Eur J Hum Genet 2009;17:434-443.
57. Kapur RP, Robertson SP, Hannibal MC *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;34:1528-1543.
58. Mousa H, Hyman PE, Cocjin J, Flores AF, Di Lorenzo C. Long-term outcome of congenital intestinal pseudoobstruction. Dig Dis Sci 2002;47:2298-2305.
59. Faure C, Goulet O, Ategbo S *et al*. Chronic intestinal pseudo-obstruction syndrome: clinical analysis, outcome, and prognosis in 105 children. French-Speaking Group of Pediatric Gastroenterology. Dig Dis Sci 1999;44:953-9.
60. Shen O, Schimmel MS, Eitan R, Granovsky-Grisaru S, Rabinowitz RR. Prenatal diagnosis of intestinal pseudo-obstruction. Ultrasound Obstet Gynecol 2007;29:229-231.
61. Weiner P, Shlum H, Ganam R, Plavnick L. Colonic pseudo-obstruction: a late complication of jejunoileal bypass. Isr J Med Sci 1984;20:405-406.

62. Amiot A, Joly F, Alves A *et al*. Long-term outcome of chronic intestinal pseudoobstruction adult patients requiring home parenteral nutrition. Am J Gastroenterol 2009;104:1262-1270.
63. Lindberg G, Iwarzon M, Tornblom H. Clinical features and long-term survival in chronic intestinal pseudo-obstruction and enteric dysmotility. Scand J Gastroenterol 2009;44:692-699.
64. De Giorgio R, Stanghellini V, Barbara G *et al*. Primary enteric neuropathies underlying gastrointestinal motor dysfunctions. Scand J Gastroenterol 2000;35:114-122.
65. Cogliandro RF, Antonucci A, De Giorgio R *et al*. Patient-reported outcomes and gut dysmotility in functional gastrointestinal disorders. Neurogastroenterol Motil 2011;23:1084-1091.
66. Lyford G, Foxx-Orenstein A. Chronic intestinal pseudo-obstruction. Curr Treat Options Gastroenterol 2004;7:317-325.
67. Pini Prato A, Rossi V, Fiore M *et al*. Megacystis, megacolon, and malrotation: a new syndromic association? Am J Med Genet 2011;155A:1798-1802.
68. de Betue CT, Boersma D, Oomen MW, Benninga MA, de Jong JR. Volvulus as a complication of chronic intestinal pseudo-obstruction syndrome. Eur J Pediatr 2011;170:1591-1595.
69. Di Nardo G, Stanghellini V, Cucchiara S et al. Enteric neuropathology of congenital intestinal obstruction: a case report. World J Gastroenterol 2006;12:5229-5233.
70. Schuffler MD, Pagon RA, Schwartz R, Bill AH. Visceral myopathy of the gastrointestinal and genitourinary tract in infants. Gastroenterology 1988;94:892-898.
71. Anuras S, Mitros FA, Soper RT *et al*. Chronic intestinal pseudo-obstruction in young children. Gastroenterology 1986;91:62-70.
72. Glassman M, Spivak W, Mininberg D, Madara J. Chronic intestinal pseudo-obstruction: a commonly misdiagnosed disease in infants and children. Pediatrics 1989;83:603-608.

73. Lapointe SP, Rivet C, Goulet O, Fekete CN, Lortat-Jacob S. Urological manifestation associated with chronic intestinal pseudo-obstruction in children. J Urol 2002;168:1768-1770.

74. Lara MC, Valentino ML, Torres-Torronteras J, Hirano M, Martí R. Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE): biochemical features and therapeutic approaches. Biosci Rep 2007;27:151-163.

75. Amiot A, Tchikviladzé M, Joly F *et al.* Frequency of mitochondrial defects in patients with chronic intestinal pseudo-obstruction. Gastroenterology 2009;137:101-9.

76. Taverna JA, Babiker HM, Yun S *et al*. The great masquerader of malignancy: chronic intestinal pseudo-obstruction. Biomark Res 2014;2:23.

77. Merlin A, Soyer P, Boudiaf M, Hamzi L, Rymer R et al. Chronic intestinal pseudo-obstruction in adult patients: multidetector row helical CT features. Eur Radiol 2008;18:1587-1595.

78. Ohkubo H, Kessoku T, Fuyuki A *et al*. Assessment of small bowel motility in patients with chronic intestinal pseudo-obstruction using cine-MRI. Am J Gastroenterol 2013;108:1130-1139.

79. Menys A, Butt S, Emmanuel A *et al*. Comparative quantitative assessment of global small bowel motility using magnetic resonance imaging in chronic intestinal pseudo-obstruction and healthy controls. Neurogastroenterol Motil 2016;28:376-83.

80. Attar A, Kuoch V, Ducreux M, Benamouzig R, Malka D. Simultaneous decompression colonoscopy and radiologic G-tube insertion in a patient with megacolon because of chronic colonic pseudo-obstruction. Gastrointest Endosc 2005;62:975-6.

81. Maqbool S, Parkman HP, Friedenberg FK. Wireless capsule motility: comparison of the SmartPill GI monitoring system with scintigraphy for measuring whole gut transit. Dig Dis Sci 2009;54:2167-2174.

82. Fell JME, 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.
83. Hyman PE, Di Lorenzo C, McAdams L *et al*. Predicting the clinical response to cisapride in children with chronic intestinal pseudo-obstruction. Am J Gastroenterol 1993;88:832-836.
84. Di Lorenzo C, Flores AF, Buie T, Hyams PE. Intestinal motility and jejunal feeding in children with chronic intestinal pseudo-obstruction. Gastroenterology 1995;108:1379-85.
85. Cucchiara S, Annese V, Minella R *et al*. Antroduodenojejunal manometry in the diagnosis of chronic idiopathic intestinal pseudoobstruction in children. J Pediatr Gastroenterol Nutr 1994;18:294-305.
86. Cucchiara S, Borrelli O, Salvia G *et al*. A normal gastrointestinal motility exclude chronic intestinal pseudo-obstruction in children. Dig Dis Sci 2000;45:258-264.
87. Amiot A, Joly F, Cazals-Hatem D *et al.* Prognostic yield of esophageal manometry in chronic intestinal pseudo-obstruction: a retrospective cohort of 116 adult patients. Neurogastroenterol Motil 2012;24:1008-e542.
88. Waseem SH, Idrees MT, Croffie JM. Neuroenteric Staining as a Tool in the Evaluation of Pediatric Motility Disorders. Curr Gastroenterol Rep 2015;17:30.
89. Angkathunyakul N, Treepongkaruna S, Molagool S, Ruangwattanapaisarn N. Abnormal layering of muscularis propria as a cause of chronic intestinal pseudo-obstruction: A case report and literature review. World J Gastroenterol 2015;21:7059-64.
90. Knowles CH, Veress B, Tornblom H *et al*. Safety and diagnostic yield of laparoscopically assisted full-thickness bowel biopsy. Neurogastroenterol Motil 2008;20:774-779.
91. Pironi L, Joly F, Forbes A *et al.* Long-term follow-up of patients on home parenteral nutrition in Europe: Implication for intestinal transplantation. Gut 2011;60:17-25.

92. Meyer R, Foong RX, Thapar N, Kritas S, Shah N. Systematic review of the impact of feed protein type and degree of hydrolysis on gastric emptying in children. BMC Gastroenterol 2015;15:137.

93. Pironi L, Arends J, Bozzetti F, *et al*; Home Artificial Nutrition & Chronic Intestinal Failure Special Interest Group of ESPEN. ESPEN guidelines on chronic intestinal failure in adults. Clin Nutr 2016;35:247-307.

94. Scolapio JS, Ukleia A, Bouras EP, Romano M. Nutritional management of chronic intestinal pseudo-obstruction. J Clin Gastroenterol 1999;28:306-312.

95. Pironi L, Spinucci G, Paganelli F *et al*. Italian guidelines for intestinal transplantation: potential candidates among the adult patients managed by a medical referral center for chronic intestinal failure. Transplant Proc 2004;36:659-661.

96. Joly F, Amiot A, Messing B. Nutritional support in the severely compromised motility patient: when and how? Gastroenterol Clin North Am 2011;40:845-851.

97. Emmanuel AV, Shand AG, Kamm MA. Erythromycin for the treatment of chronic intestinal pseudo-obstruction: description of six cases with a positive response. Aliment Pharmacol Ther 2004;19:687-694.

98. Rao AS, Camilleri M. Review article. Metoclopramide and tardive dyskinesia. Aliment Pharmacol Ther 2010;31:11-19.

99. Soudah HC, Hasler WL, Owyang C. Effect of octreotide on intestinal motility and bacterial overgrowth in scleroderma. N Engl J Med 1991;325:1461-1467.

100. Verne GN, Eaker EY, Hardy E, Sninsky CA *et al*. Effect of octreotide and erythromycin on idiopathic and scleroderma-associated intestinal pseudoobstruction. Dig Dis Sci 1995;40:1892-1901.

101. Gmora S, Poenaru D, Tsai E. Neostigmine for the treatment of pediatric acute colonic pseudo-obstruction. J Pediatr Surg 2002;37:E28.

102. Calvet X, Martinez JM, Martinez M. Repeated neostigmine dosage as palliative treatment for chronic colonic pseudo-obstruction in a patient with autonomic paraneoplastic neuropathy. Am J Gastroenterol 2003;98:708-709.

103. O'Dea CJ, Brookes JH, Wattchow DA. The efficacy of treatment of patients with severe constipation or recurrent pseudo-obstruction with pyridostigmine. Colorectal Dis 2010;12:540-8.

104. Sanger GJ. Translating 5-HT receptor pharmacology. Neurogastroenterol Motil 2009;21:1235-1238.

105. Camilleri M, Deiteren A. Prucalopride for constipation. Expert Opin Pharmacother 2010;11:451-461.

106. Emmanuel AV, Kamm MA, Roy AJ, Kerstens R, Vandeplassche L. Randomised clinical trial: the efficacy of prucalopride in patients with chronic intestinal pseudoobstruction- a double-blind, placebo-controlled, cross-over, multiple n = 1 study. Aliment Pharmacol Ther 2012;35:48-55.

107. Husebye E. Gastrointestinal motility disorders and bacterial overgrowth. J Intern Med 1995;237:419-427.

108. Cuoco L, Montalto M, Jorizzo RA *et al*. Eradication of small intestinal bacterial overgrowth and oro-cecal transit in diabetics. Hepatogastroenterology 2002;49:1582-1586.

109. Madrid AM, Hurtado C, Venegas M, Cumsille F, Defilippi C. Longterm treatment with cisapride and antibiotics in liver cirrhosis: effect on small intestinal motility, bacterial overgrowth, and liver function. Am J Gastroenterol 2001;96:1251-1255.

110. Singh VV, Toskes PP. Small bowel bacterial overgrowth: presentation, diagnosis, and treatment. Curr Gastroenterol Rep 2003;5:365-372.

111. Pimentel M. Review of rifaximin as treatment for SIBO and IBS. Expert Opin Investig Drugs 2009;18:349-358.

112. Gomez R, Fernandez S, Aspirot A *et al*. Effect of amoxicillin/clavulanate on gastrointestinal motility in children. J Pediatr Gastroenterol Nutr 2012;54:780-784.

113. 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;28:722-725.

114. Geller A, Petersen BT, Gostout CJ. Endoscopic decompression for acute colonic pseudo-obstruction. Gastrointest Endosc 1996;44:144-150.

115. Chun C, Aulakh S, Komlos F, Triadafilopoulos G. Tube to freedom: use of a venting jejunostomy in a patient with chronic intestinal pseudo-obstruction. Dig Dis Sci 2012;57:3076-3079.

116. Kim JS, Lee BI, Kim BW. Repetitive Colonoscopic Decompression as a Bridge Therapy before Surgery in a Pregnant Patient with Chronic Intestinal Pseudo-Obstruction. Clin Endosc 2013;46:591-594.

117. Küllmer A, Schmidt A, Caca K. Percutaneous endoscopic cecostomy (introducer method) in chronic intestinal pseudo-obstruction: Report of two cases and literature review. Dig Endosc 2016;28:210-5.

118. Murr MM, Sarr MG, Camilleri M. The surgeon's role in the treatment of chronic intestinal pseudo-obstruction. Am J Gastroenterol 1995;90:2147-51.

119. Sabbagh C, Amiot A, Maggiori L *et al*. Non-transplantation surgical approach for chronic intestinal pseudo-obstruction: analysis of 63 adult consecutive cases. Neurogastroenterol Motil 2013;25:680-686.

120. Pakarinen MP, Kurvinen A, Koivusalo AI *et al*. Surgical treatment and outcomes of severe pediatric intestinal motility disorders requiring parenteral nutrition. J Ped Surg 2013;48:333-338.

121. Irtan S. Bellaïche M, Brasher C *et al*. Stomal prolapse in children with chronic intestinal pseudo-obstruction: a frequent complication ? J Ped Surg 2010;45:2234-2237.

122. Millar AJ, Gupte G, Sharif K. Intestinal transplantation for motility disorders. Semin Pediatr Surg 2009;18:258-262.

123. Lao OB, Healey PJ, Perkins JD *et al*. Outcomes in children after intestinal transplant. Pediatrics 2010;125, 550-558.

124. Masetti M, Di Benedetto F, Cautero N *et al*. Intestinal transplantation for chronic intestinal pseudo-obstruction in adult patients. Am J Transplant 2004;4:826-9.

125. Tzakis AG, Kato T, Levi DM *et al*. 100 multivisceral transplants at a single center. Ann Surg 2005;242:480-93.

126. Sudan DL, Chinnakotla S, Horslen S *et al*. Basiliximab decreases the incidence of acute rejection after intestinal transplantation. Transplant Proc 2002;34:940-1.

127. Lauro A, Zanfi C, Pellegrini S *et al*. Isolated intestinal transplant for chronic intestinal pseudo-obstruction in adults: long-term outcome. Transplant Proc 2013;45:3351-5.

128. Lauro A, Zanfi C, Dazzi A *et al*. Disease-related intestinal transplant in adults: results from a single center. Transplant Proc 2014;46:245-8.

129. Ceulemans LJ, Monbaliu D, De Roover A *et al*. Belgian multicenter experience with intestinal transplantation. Transpl Int 2015;28:1362-70.

130. Colledan M, Stroppa P, Bravi M *et al*. Intestinal transplantation in children: the first successful Italian series. Transplant Proc 2010;42:1251-1252.

131. Halter JP, Michael W, Schüpbach M *et al.* Allogeneic haematopoietic stem cell transplantation for mitochondrial neurogastrointestinal encephalomyopathy. Brain 2015;138:2847-58.

132. De Giorgio R, Pironi L, Rinaldi R *et al.* Liver transplantation for mitochondrial neurogastrointestinal encephalomyopathy. Ann Neurol 2016 Epub ahead of print.

Tables

Table 1. Etiology and classification of CIPO.

Primary	Secondary	Familial forms
• No demonstrable etiopathogenetic causes	• Neurological disorders • Metabolic diseases • Paraneoplastic syndromes • Neurotropic viruses • Autoimmune disorders • Celiac disease • Neuro-muscular disorders • Radiation enteritis • Endocrinological disorders • Drugs	• **Autosomal dominant** ✓ *SOX 10** • **Autosomal recessive** ✓ *RAD21** ✓ *SGOL1** ✓ *TYMP** ✓ *POLG** • **X-Linked** ✓ *FLNA** ✓ *L1CAM**

Notes: *, denotes mutation(s) to the indicated genes. *FLNA*, filamin; L1CAM, L1 cell adhesion molecule; *POLG*, polymerase DNA gamma; *RAD21*, cohesin complex component; *SGOL1*, shugoshin-like 1; *SOX10*, SRY-BOX 10; *TYMP*, thymidine phosphorylase.

Table 2. Main similarities and differences of CIPO in children and adults.

	Children	Adults
Etiology	Mainly idiopathic	Half of cases are secondary to acquired diseases.
Histopathology	Myopathies and neuropathies	Mainly neuropathies.
Symptom onset	In utero, from birth or early infancy with 65-80% of patients symptomatic by 12 months of age	Median age of onset at 17 years.
Clinical features	Occlusive symptoms at birth and/or chronic symptoms without free intervals Urological involvement is commonly encountered ranging from 36-100% pediatric case series High risk of colonic and small bowel volvulus secondary to severe gut dilation, dysmotility, congenital bridles or concurrent malrotation	Chronic abdominal pain and distension with superimposed acute episodes of pseudo-obstruction. Urinary bladder involvement not so often reported
Natural history	Myopathic CIPO, urinary involvement and concurrent intestinal malrotation are poor prognostic factors	The ability to restore oral feeding and the presence of symptoms < 20 years of age is associated with a low mortality; while, systemic sclerosis and severe/diffuse esophageal and intestinal dysmotility are associated with a high mortality
Diagnostic approach	Specialized tests (e.g. intestinal manometry) often difficult to perform; non-invasive, radiation-free imaging tests are warranted	Various methodological approaches usually starting from endoscopy and radiological tests up to more sophisticated functional exams
Nutritional therapy	To ensure normal growth extensively hydrolysed and elemental formulas are often empirically used to facilitate intestinal absorption	To improve nutritional status and prevent malnutrition
Pharmacological therapy	Small number / sample size controlled trials	Small number / sample size controlled trials; few conclusions can be drawn for most drugs.
Surgical therapy	Venting ostomies (although characterized by high complication rates) possibly helpful; surgery as a 'bridge' to transplantation may be indicated in highly selected cases	Venting ostomies can be helpful; resective surgery may be indicated in accurately selected patients (i.e. cases with proven segmental gut dysfunction)

Table 3. Compounds used for the treatment of CIPO in isolated cases or in small series of pediatric and adult patients.

Drug and study	Type of study	Number and type of patients	Dose and period of treatment	Results	Side effects
Erythromycin					
Emmanuel et al. APT 2004	Retrospective case series	15 adults	1.5-2 g/day, oral or i.v.	6 responders (4 myopathy)	Not reported
Metoclopramide	No reported studies	----------	----------	----------	--------
Domperidone	No reported studies	----------	----------	----------	--------
Octreotide					
Soudah et al. N Eng J Med 1991	Case series	5 adults with scleroderma related CIPO and SIBO	100 mcg/day sc	reduces SIBO and improved symptoms	Not reported
Verne et al. Dig Dis Sci 1995	Prospective case series	14 adults	50 mcg/day sc, 20-33 weeks in association with erythromycin	5 responders	Not reported
Neostigmine					
Calvet et al. Am J Gastroenterol 2003	Case report	1 adult with chronic colonic pseudo-obstruction with autonomic paraneoplastic neuropathy	2 mg i.v. every 6 hours	Improvement of abdominal distension and discomfort and enteral diet could be resumed	Not reported
Pyridostigmine					
O'Dea et al. Colorectal Dis 2010	Case series	7 adults	10 mg b.i.d. and increased if required (max 30 mg) orally	7 responders	Not reported
Prucalopride					
Emmanuel et al. APT 2012	RCT cross-over trial	4 adults	2-4 mg	3 responders	Not reported
Antibiotics	No reported studies	----------	----------	---------	----------
Non-narcotic pain modulators	No reported studies	----------	----------	---------	----------
Buprenorphine					
Prapaitrakool et al. Clin J Pain 2012	Case Series	4 children	10-15 mcg/h, transdermal, 1-3 years	3 responders	Pruritus and erythema on the application site

Figure Legends

Figure 1

Synoptic view of the CIPO spectrum.

A-B: illustrate the most severe pediatric cases with antenatal (*in utero*) evidence of multivisceral dilation (ultrasound picture A - from ref 60) i.e. often gut (B) and urinary system, commonly associated with an extremely poor prognosis.

C-D: exemplify the CIPO phenotype with a rapid progression to intestinal dilatation (± urether / bladder) and failure often occurring as a result of an anamnestically reported gastroenteritis. Specifically, C depicts one of such case with massive bowel dilatation at the operative room and histopathology (inset to figure D) revealed an intense inflammatory (mainly lymphocytic) neuropathy (hence, myenteric ganglionitis. Alkaline phosphatase antialkaline phosphatase immunohistochemical technique using specific anti-CD8 monoclonal antibodies to identify a subset of T lymphocytes).

E-G: are representative examples of another phenotype of the syndrome which may be observed in patients who experience more insidious mild and nonspecific symptoms progressing up to a classic CIPO over time. E shows a markedly distended abdomen of a 32-year old male patient who presented with a sub-occlusive episodes after some years of unspecific (dyspeptic-/irritable bowel syndrome-like) symptoms. Note the evident air-fluid levels detectable in up-right position at a conventional plain abdominal X-ray (F and G, antero-posterior and latero-lateral view, respectively).

Figure 2

Manometric findings in CIPO.

A: illustrates a monotonous pattern of phasic and tonic contractions in the small bowel of a 3-year old boy with a congenital CIPO. No migrating motor complexes (MMC) were detected during a 4-hour fasting study.

B: shows an abnormal migration of the phase 3 of the MMC with a simultaneous component in the duodenum in a 7-year old girl affected by a non-congenital form of CIPO.