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REVIEW

Pharmacological and nutritional therapy of children and adults with chronic intestinal pseudo-obstruction

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ABSTRACT

Introduction: Chronic intestinal pseudoobstruction (CIPO) is a rare, heterogenous, and severe form of gastrointestinal dysmotility.

Areas covered: Pertinent literature on pediatric and adult CIPO management has been assessed via PubMed, Scopus, and EMBASE from inception to June 2022. Prokinetics, aimed at restoring intestinal propulsion (e.g. orthopramides and substituted benzamides, acetyl cholinesterase inhibitors, serotonergic agents, and others), have been poorly tested and the available data showed only partial efficacy. Moreover, some prokinetic agents (e.g. orthopramides and substituted benzamides) can cause major side effects. CIPO-related small intestinal bacterial overgrowth requires treatment preferably via poorly absorbable antibiotics to avoid bacterial resistance. Apart from opioids, which worsen gut motility, analgesics should be considered to manage visceral pain, which might dominate the clinical manifestations. Nutritional support, via modified oral feeding, enteral, or parenteral nutrition, is key to halting CIPO-related malnutrition.

Expert opinion: There have been significant roadblocks preventing the development of CIPO treatment. Nonetheless, the considerable advancement in neurogastroenterology and pharmacological agents cast hopes to test the actual efficacy of new prokinetics via well-designed clinical trials. Adequate dietary strategies and supplementation remain of crucial importance. Taken together, novel pharmacological and nutritional options are expected to provide adequate treatments forthese patients.

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1. Introduction

Chronic intestinal pseudoobstruction (CIPO) is a severe gut motility disorder covering the wide heterogeneous spectrum of changes affecting the structure and/or function of the gastrointestinal (GI) neuromuscular components [1,2]. From a functional standpoint, the motor impairment in CIPO patients is too severe to mimic an obstructive episode in the absence of demonstrable anatomical causes. This definition can be applied to both adult and pediatric CIPO, with the latter bearing the acronym of PIPO (i.e. pediatric intestinal pseudoobstruction) as proposed by a recent consensus paper [1,2]. Both PIPO and CIPO are rare diseases and so far, there are no clear epidemiological data. It has been estimated that in the USA about 100 infants per year are affected by intestinal pseudoobstruction; the incidence among adults is 0.2 (male) and 0.24 (female) per 100.000 patients/year [3–5]. A Japanese survey observed a prevalence of 3.7 in one million children (1 in 270.000 children <15 years of age) with no gender differences [6]. However, since symptoms are nonspecific and often physicians fail to establish an early diagnosis, the prevalence and incidence of PIPO/CIPO remain unclear [7,8].

A wide array of *noxae* may affect the integrity of each control system of the GI tract, namely intrinsic or extrinsic nerves supplying the gut (hence neuropathy), the normal architecture of the smooth muscle cells (myopathy) and/or interstitial cells of Cajal (ICC), which act as pacemaker cells rhythmicity and/or mechanosensory transduction of the GI tract (mesenchymopathy). These changes, individually or in combination, generate severe dysmotility in intestinal pseudoobstruction. Although the small bowel and colon are the most commonly affected segments, the whole GI tract can be involved in PIPO/CIPO, leading to a severe impairment of GI propulsion and potentially lethal complications (e.g. dehydration and electrolyte imbalance, ischemia/perforation, and severe malnutrition) [9–13]. Both PIPO/CIPO can be classified in primary forms or idiopathic (no apparent cause underlying dysmotility) and secondary forms associated with many different systemic disorders. Some forms of PIPO/CIPO can be genetic in origin and recognize an autosomal dominant (*SOX10*) or a recessive transmission (*RAD21, SGOL1, TYMP, and POLG*) or X-linked conditions (*FLNA, L1CAM*) [14].

Because of heterogeneous pathogenetic mechanisms, the diagnosis of PIPO should require at least two out of four of the

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Article highlights

- The pharmacological and nutritional treatments of pediatric and adult chronic intestinal pseudo-obstruction (PIPO/CIPO, respectively) remain challenging.
- Prokinetics, e.g. orthopramides and substituted benzamides, acetyl cholinesterase inhibitors, and serotonergic agents, yielded only partial results in improving intestinal propulsion and controlling dysmotility-related symptoms.
- Abdominal pain and distension (along with bloating) are usually severe symptoms/signs in PIPO/CIPO patients and require pharmacological (avoiding opioids)/non-pharmacological (endoscopic decompressive measures) anti-nociceptive strategies.
- Small intestinal bacterial overgrowth (SIBO) should be managed by using poorly absorbable antibiotics and prokinetic drugs. In line with this, in patients with mild forms of PIPO/CIPO dietary indications should be advised (i.e. low-sugar, -fibre and -fat diet).
- Each patient should be evaluated by a multi-disciplinary team (including nutritionists and dieticians) to establish an individualized stepwise dietary/nutritional strategy (from oral to enteral/parenteral nutrition).
- Significant changes are awaited in the treatment strategies hopefully improving quality and life expectations of PIPO/CIPO patients.

following criteria: *i*) Objective measure of small intestinal neuromuscular involvement (manometry, histopathology, and transit); *ii*) Recurrent and/or persistently dilated loops of small intestine with air fluid levels; *iii*) Genetic and/or metabolic abnormalities definitively associated with PIPO; and *iv*) Inability to maintain adequate nutrition and/or growth on oral feeding (needing specialized enteral nutrition and/or parenteral nutrition support) [1]. Concerning CIPO, in the absence of consensus papers, the following criteria can be used: a) exclusion of mechanical obstruction; b) motility recordings, preferably small intestinal motility recordings show evidence of a motility disorder and c) when possible full thickness biopsy indicative of neuro-mesenchymo(interstitial cells of Cajal)-myopathy [15].

Symptoms of PIPO/CIPO often mimic those of functional GI disorders. The most common symptoms in these patients include abdominal pain, bloating, vomiting, constipation, and diarrhea [16].

Ideally, the pharmacological treatment is aimed at improving/restoring a sufficiently effective motility to minimize the disabling symptoms/signs and bacterial overgrowth thereby reducing the high morbidity of these patients [3,7,8,16–20]. In the most severe cases, digestive motility disorders are associated with involvement of the urinary tract and afferent neural pathways since intractable visceral pain is most likely of neuropathic origin. Furthermore, the inability to maintain an adequate nutritional status requires dietary actions (modified oral diets) and nutritional interventions (from enteral to parenteral support depending on the severity of gut dysfunction) in order to contrast growth failure and severe malnutrition, common features in PIPO and CIPO. Further, to idiopathic forms, secondary PIPO/CIPO should be carefully considered according to an in-depth diagnostic work-up aimed to identify immune-mediated connective tissue disorders (e.g. scleroderma, polymyositis/dermatomyositis, systemic lupus erythematosus, and others); metabolic/endocrine (diabetes mellitus, hyper-, hypothyroidism, hyperparathyroidism; porphyria, etc.); either degenerative (e.g. Parkinson's disease) or inflammatory (paraneoplastic syndromes) neurological disorders; and infectious (Chagas' disease, neurotropic viruses, etc.). A detailed analysis of treatment options for secondary PIPO/CIPO would require specific coverage, which falls beyond the scope of the present article (the reader is referred to other reviews, e.g. see [21]).

This review aims to provide a thorough update on the therapeutic options ranging from pediatric to adult idiopathic pseudo-obstruction, focusing on pharmacological options and nutritional approaches.

2. Search strategy

PubMed, Scopus, and EMBASE were searched from inception to June 2022. The search terms were "chronic intestinal pseudo-obstruction' OR 'pediatric intestinal pseudo-obstruction' OR 'Severe intestinal dysmotility' AND 'children' AND 'therapy' AND 'antibiotics' AND 'nutrition' AND 'prokinetics.' In addition, we expanded our analysis through a manual search of references of included studies and previous reviews.

3. Body

The next paragraphs will detail the main aspects of PIPO/CIPO conservative management, which includes pillars such as pharmacological and nutritional approaches.

3.1. Pharmacological treatment

Data about the efficacy of various treatments in pseudo-obstruction are generally scanty and mainly derived from studies on adult patients. Furthermore, data in pediatric patients have been hampered by side effects evoked by some drugs (e.g. metoclopramide), which may occur more frequently than in adults [22]. The most commonly used pharmacological options include prokinetic agents (e.g. metoclopramide, domperidone, motilides, anticholinesterases, 5-hydroxytryptamine [5-HT]/serotonergic drugs mainly acting through the receptor subtype 5-HT4) (Table 1) and antiemetics, such as anti-dopaminergic agents (metoclopramide, domperidone) and 5-HT3 antagonists (ondansetron/granisetron) [23–26]. Antibiotics represent another treatment milestone directed to contrast small intestinal bacterial overgrowth (SIBO) or, broadly, gut dysbiosis secondary to the severe motility impairment. SIBO may cause diarrhea, abdominal distension, and pain along with loss of a wide number of key elements and hydrophilic vitamins (i.e. B1, B2, B3, B5, B6, B9, B12, and C), which contribute to malnutrition in PIPO/CIPO. Finally, since visceral pain is one of the most common and disabling symptoms, the management should consider anti-nociceptive drugs with a cautionary approach to opioids, known to be detrimental for gut motility. By improving GI propulsive motility, the pharmacological treatment may integrate dietary strategies in maintaining an acceptable nutritional status and improving quality of life of PIPO/CIPO patients [14,19,21].

Table 1. Prokinetics so far investigated in patients with chronic intestinal pseudo-obstruction (CIPO) main clinical features and treatment options.

References (year)	Study type	Number of patients	Patient demographic and gender	CIPO phenotype/ etiology	Dose and treatment duration	Outcomes	Findings	Reported side effects
Prokinetics								
Orthopramides: *(metoclopramide and domperidone)*								
Metoclopramide Lipton AB, Knauer CM (1977) [21]	Double-blind trial	1	23 yr-old female	Idiopathic	4 courses of 28 days (10 mg 4 times/day or placebo)	Number of days of hospitalization during each 28-day course; weight gain; daily record of symptoms	No beneficial *vs.* placebo	Not reported
Hirsh EH et al. (1981) [27]	Case series	4 cases treated with metoclopramide out of 11 CIPO patients	Mean age 53 yrs; 5 females and 6 males	2 scleroderma-associated; 2 idiopathic; 7 undefined	Not reported	Improvement of symptoms	Beneficial effects in 2 out of 4 treated patients	Not reported
Domperidone Turgeon DK (1990) [28]	Case report	1	75 yr-old male	Neurogenic (underlying neuronal intestinal dysplasia)	10 mg 4 times/day for 2 months	Improvement of symptoms; weight gain	Resolution of abdominal pain; decreased vomiting; weight gain (>1.36 kg); increased appetite	Not reported
Acetyl cholinesterase inhibitors (ACIs)								
Pyridostigmine	Observational study/case series	13	Age range 24–59 yrs for STC; 22–80 for intestinal pseudo-obstruction	6 patients with STC; 7 intestinal pseudo-obstruction (4 chronic and 3 acute)	10–30 mg 2 time/day for both STC and intestinal pseudo-obstruction	Symptom improvement	1 out of 6 patients with STC reported improvement of symptoms; all 7 patients with intestinal pseudo-obstruction had symptom improvement	Not reported
O'Dea CJ et al. 2010 [41]		1			30 mg/kg/day	Symptom improvement		Not reported
Boybeyi O et al. 2009 [42]	Case report	1		Neuropathic	0.5 mg/kg 2 times/day and increased to 1 mg/kg 2 times/day; increased up to	Evaluation of improvement of sign and symptoms (e.g. abdominal distension)		Not reported
Choudhury A et al. (2018) [43]	Case report	2		Myopathic	1.5 mg/kg 2 times/day after 7 months	Symptom improvement	Resolution of abdominal distention, improved oral intake and increased bowel movement frequency	Not reported
Manini ML et al. (2018) [44]	Case series	1	3 yr-old male	Neuropathic	0.25 mg/kg/day in 2 doses, increased up to 0.3 mg/kg/day over the next 2 yrs	Efficacy of the treatment	Improvement of spontaneous bowel movements and volume of gastric drainage	Not reported
Lee H et al. (2019) [45]	Case report		9 yr-old female	Myopathic (ACTG2 mutations)	Oral pyridostigmine180 mg/day (case 1); 7 mg/kg/day (case 2)	Symptom improvement	Decreased abdominal distention, increased enteral calories, and decreased PN	Not reported
Di Nardo G et al. (2019) [46]			18 yr-old male	Idiopathic	2 mg/kg 2 times/day gradually increased to 3 mg/kg 2 times/day		Reduced length of hospital stay and dependency on PN	Not reported
			11 yr-old female; 5 yr-old female				Resolution of vomiting, reduction of abdominal distension, occurrence of spontaneous bowel movements	Not reported
			2 yr-old female					Not reported
Serotonergic agents								
Prucalopride Emmanuel AV et al. (2012) [66]	Double-blind, randomized, placebo-controlled, cross-over trial	7	Mean age 39 yrs; 5 females	4 visceral neuropathy, 3 visceral myopathy	12-week treatment periods of either prucalopride (2–4 mg) or placebo/day	Symptom improvement	Beneficial effects on pain in 3 patients, nausea in 2, vomiting in 1, bloating in 4, and reduced analgesic intake in 2	Not reported

(*Continued*)

Table 1. (Continued).

References (year)	Study type	Number of patients	Patient demographic and gender	CIPO phenotype/ etiology	Dose and treatment duration	Outcomes	Findings	Reported side effects
Erythromycin	Case series	16	Mean age 8.7 yrs; 8 females	6 GE reflux, 4 cycling vomiting, 3 gastroparesis, 2 CIPO and 1 Crohn's disease	1 mg/kg followed by 0.5 g/kg of octreotide	Increase in the number of phase 3 of MMC	Phase 3 occurred in 12 out of 16 patients after erythromycin administration	Not reported
Di Lorenzo et al. (1999) [19]	Case report	1	67 yr-old male	Idiopathic	900 mg/day for 2 weeks followed by 400 mg/day for 12 weeks	Improvement of symptoms and intestinal transit	Beneficial effects on postprandial abdominal distention, nausea, vomiting; improvement of intestinal transit	Abdominal pain
Minami T et al. (1996) [71]	Case series	15	Mean age 35 yrs; 7 males and 8 females	14 idiopathic (visceral myopathy, neuropathy and undefined); 1 secondary to scleroderma	1.5–2 g/day	Number and severity of obstructive episodes	6 patients had decreased severity and frequency of episodes	Not reported
Emmanuel AV et al. (2004) [77]								
Octreotide	Case series	11	Mean age 62 yrs; 2 females (among patients with scleroderma-related CIPO)	5 scleroderma-related CIPO (and 6 healthy volunteers)	100 g/day for scleroderma-related CIPO; 10 g/day for healthy volunteers	SIBO improvement in scleroderma-related CIPO; increase phase 3 in healthy volunteers	Symptom and breath test improvement in all scleroderma-related CIPO; enhanced intestinal motility in healthy volunteers	Not reported
Soudah HC et al. (1991) [86]	Clinical trial	14		5 scleroderma and 9 idiopathic	Combination of oral erythromycin 200 mg 3 times/ day and subcutaneous octreotide 50 µg at night time, for a mean follow-up of 20–33 weeks	Clinical response	5 patients had improvement of nausea and abdominal pain	Not reported
Verne GN et al. (1995) [88]	Case report	1		Scleroderma-related CIPO		Clinical improvement	Successful treatment	Not reported
Lanting PJ et al. (1993) [89]	Case series	7	Age range 34–82 yrs; 13 females	3 with scleroderma-related CIPO; 4 with diffuse systemic sclerosis		Symptom improvement	All patients responded to octreotide with reduction of symptom severity	Not reported
Nikou GC et al. (2007) [91]	Case series	3				Symptom improvement	Improvement of symptoms	4 had adverse manifestations (1 allergic reaction; 1 hyperglycemia; 1 hypertension; 1 pancreatitis)
Perlemuter G et al. (1999) [92]	Retrospective open-label study	16	Not reported	Sjogren syndrome; SLE; and systemic sclerosis	Not reported	Utility of long-term daily use of octreotide on tolerance of enteral feeding in PN-dependent children with CIPO.	Increased enteral feeding tolerance in 11 out of 16 patients	
Ambartsumyan L et al. (2016) [96]			Age range 37–64 yrs; 7 females		0.1 mg 2 times/day SC or 20 mg/ month IM			
			Mean age 47 yrs; 3 females	5 idiopathic; 8 mitochondriopathy; 2 short bowel; 1 post-surgical	50 g 2 times /day for 12 months (for patient n. 2 octreotide dose was increased up to 200 mg 2 times/day)			
			Mean age 5 yrs; 14 females		0.5–1 g/kg/day 2 times/day			

Notes: CIPO: chronic intestinal pseudo-obstruction; GE: gastroesophageal; IM: intramuscular; MMC: migrating motor complex; PN: parenteral nutrition; SC: subcutaneous; SLE: systemic lupus erythematosus; STC: slow transit constipation; yr/yrs: year/years.

3.1.1. Prokinetics

This term applies to medications that are able to enhance and coordinate muscular contractions along the GI tract, thereby leading to an overall propulsive effect on intra-luminal contents. Notably, some prokinetics are active in selective segments of the GI tract, whereas others exhibit a more generalized effect, which is often the result of a widespread distribution of receptors targeted by the pharmacological compound [26]. Despite important achievements in the treatment of GI dysmotility, there are still large unmet needs, which urge further developments. The following is an appraisal of the main classes of prokinetics and their effects in PIPO/CIPO patients.

3.1.1.1. Orthopramides and substituted benzamides.

Dopamine is a neurotransmitter able to inhibit acetylcholine release by enteric neurons leading to a decreased GI motility (mainly in the gastric antrum and proximal small intestine). Metoclopramide and domperidone counteract the dopamine inhibitory effect by acting as dopamine 2 receptor (D2) antagonists, which enhance antro-duodenal motility [27]. Both metoclopramide and domperidone were widely used in patients with functional upper GI disorders and gut dysmotility (e.g. functional dyspepsia and gastroparesis) since 2013, when they were declared off label (in Europe) for these indications.

Data on metoclopramide and domperidone in CIPO are scanty, being limited to three studies showing only marginal efficacy on symptoms [22,28,29]. A possible indirect application of these drugs in CIPO patients is related to their anti-emetic properties exerted by acting both peripherally and directly on D2 receptors expressed by neurons of the chemoreceptor trigger zone, which lies in the central nervous system (but outside the blood-brain barrier) and detects blood-borne emetogenic stimuli. In clinical practice, metoclopramide is used from 20 to 30 mg subdivided in 2–3 doses/day for a maximum of three days (according to the Food and Drug Administration, FDA). In addition to oral and parenteral formulations, an intra-nasal metoclopramide has been recently approved. Domperidone is recommended at 10 mg (up to 20 mg) three times per day for one week; its use in pediatric patients is contraindicated, especially if body weight is below 35 kg or age <12 years [29]. Both metoclopramide and domperidone raised considerable concerns in terms of safety. Specifically, metoclopramide, which easily crosses the blood-brain barrier, has a boxed warning by the FDA due to the risk of neurological side effects, including extrapyramidal disorders and tardive dyskinesia [27,30]. Also, the risk of QT-interval prolongation and related life-threatening cardiac dysrhythmias can be ascribed to both drugs [31]. In Europe, domperidone is not any longer available as over-the-counter compound, being restricted by medical prescription. In patients with a corrected QT-interval >470 ms (in males) and >450 ms (in females) domperidone is contraindicated [32].

3.1.1.2. Acetyl cholinesterase inhibitors (ACIs).

Acetylcholine and tachykinins are the main excitatory neurotransmitter in the GI tract. Acetyl cholinesterase inhibitors (ACIs), i.e. neostigmine and pyridostigmine, promote propulsive GI motility by preventing the degradation of acetylcholine and increasing its concentration in the synaptic cleft [33,34]. Intravenous neostigmine has proven efficacy in pediatric and adult acute colonic pseudo-obstruction (ACPO or Ogilvie syndrome) [35–37]. A meta-analysis of four studies evaluating 127 patients with ACPO who failed to respond to conservative management showed that neostigmine (2–5 mg i.v.) was effective in reducing colonic diameters in 89% of cases *vs*. 14.7% of the control group. The main side effects recorded in these studies included abdominal pain (53%), sialorrhea (31%), vomiting (16%), and bradycardia (6%) [35]. In children with hematologic malignancies and ACPO, neostigmine 0.01 mg/kg (up to 0.5 mg) twice daily for a total of 5 doses has been successfully used without side effects [38]. Repeated doses of neostigmine were successful in the treatment of an adult patient with colonic CIPO [39] (an example of the prokinetic action of neostigmine has been illustrated in Figure 1). Chronic use in children with CIPO has not been reported yet. Chronic treatment with neostigmine of PIPO/CIPO patients remains largely debated and should be probably reserved to those cases intolerant to oral ACIs.

Pyridostigmine, an orally longer acting reversible ACI, has been successfully used in seven adult patients with CIPO who

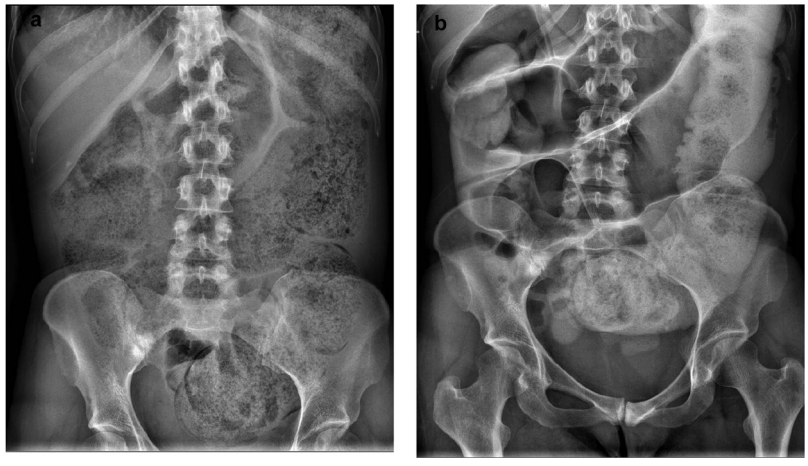

Figure 1. X-ray of the abdomen showing a massive stool impaction in the colon (1A) of a 36-yr old female patient with idiopathic chronic intestinal pseudo-obstruction. Following intravenous neostigmine (0.5 mg 3 times/day) for 3 days there was a considerable reduction of bowel dilatation and intracolonic stool content (1B) most likely related to the prokinetic effect of this drug.

failed standard therapies [40] and in six pediatric patients [41–45] (see Table 1 for details).

As a practical note, pyridostigmine in the range of 0.25 mg/kg/day (in a single dose) up to 7.0 mg/kg/day (divided in two to three doses), should be recommended. A 'step-up' increase is advisable in patients with PIPO/CIPO, whereas 'bottom-down' strategy is thought to be more appropriate in patients with acute forms of pseudo-obstruction dominated by massive bowel loop dilatation. The risk of side effects increases with dose increment. The most common side effects of pyridostigmine include nausea, vomiting, abdominal cramps, diarrhea, and sialorrhea. Other less common side effects include muscle weakness/fasciculations/cramps, miosis, hypersensitivity reactions, urinary frequency, and bronchial hypersecretion [46]. Bradycardia is a rare but possible side effect and predisposed patients should be monitored in this respect.

3.1.1.3. Serotonergic agents. The gut is the most important depot of 5-HT/serotonin, a bioactive amine synthesized and stored in enterochromaffin cells widely distributed throughout the mucosa of the GI tract. Serotonin is also contained in a few interneurons of the enteric nervous system [47]. Serotonin is a major signaling molecule in the gut-brain axis and exerts its actions by interacting with seven main receptor subtypes [48], which are involved in the control of various physiological functions, such as GI secretion, sensation, and motility [49]. One of these receptor subtypes, the 5-HT4, has been shown to promote intestinal motility [49]. Several agonists developed for this receptor showed efficacy in improving PIPO/CIPO-related symptoms and gut motility, although limited by poor selectivity, causing serious adverse events. A typical example of nonselective 5-HT4 agonists was cisapride, largely used as a valuable prokinetic drug in clinical practice, until data showed that it inhibited the human ether-à-go-go-related (hERG) potassium channel leading to life-threatening cardiac arrhythmias. Thus, cisapride has been withdrawn from the market in the 2000 with a minimal availability as a compassionate use [50,51]. Tegaserod, an aminoguanidine indole derivative of serotonin, is another nonselective 5-HT4 (partial) agonist, which has been associated with cardiovascular and cerebrovascular ischemic events, likely through the 5-HT1D and 5-HT2B receptor interaction [52,53]. Tegaserod has been withdrawn from the market in 2007; however, for its significant efficacy over placebo in constipated irritable bowel syndrome (IBS), the FDA decided to reapprove this drug for women under the age of 65 years and without cardiovascular risk factors [53]. Tegaserod has never been tested in patients with PIPO/CIPO.

New highly selective 5-HT4 agonists, such as prucalopride, velusetrag, naronapride, and others, are now available [54–56]. Among these new drugs, only prucalopride has been approved by the European Medicines Agency (EMA) and FDA. This is a selective, high-affinity 5-HT4 receptor agonist facilitating cholinergic neurotransmission. Prucalopride is well absorbed from the GI tract, with an oral bioavailability of >90%. The highest concentration is reached within 2–3 hours from a single oral administration and plasma half-life is estimated to be 30 hours. Concomitant intake of food has no effect on prucalopride bioavailability. In children, the pharmacokinetic profile of a single oral solution of prucalopride (0.03 mg/kg) shows comparable results to that of adults [57]. Notably, compared to cisapride and tegaserod, prucalopride at therapeutic concentrations does not interact with cardiac hERG channel and 5-HT1B/D receptors and exhibits a > 150-fold higher affinity for 5-HT4 than other serotonin receptors [58,59]. In addition, prucalopride does not show clinically relevant hemodynamic or electrocardiographic changes [60]. These safety data have been confirmed in a cardiovascular high-risk elderly population [58]. Prucalopride shows significant prokinetic effects throughout the GI tract, including acceleration of gastric emptying, small bowel, and colonic transit in healthy volunteers [61,62] and in patients with functional constipation [54]. Prucalopride has been approved by EMA and FDA for the symptomatic treatment of chronic constipation in patients in whom laxatives failed to provide adequate relief [56]. In the three pivotal clinical trials on chronic constipation, prucalopride at 2 and 4 mg/day for 12 weeks resulted in a significantly higher proportion of patients reaching the primary efficacy endpoint, i.e. ≥3 spontaneous complete bowel movements/week compared to placebo. Other secondary endpoints, including overall improvement of bowel habit and associated symptoms, patient satisfaction with bowel habit and treatment and quality of life in patients with severe chronic constipation, were also reached [63–65]. The most common side effects occur mainly during the first day of treatment and include headache (decreasing up to disappearing in the subsequent days of treatment), nausea, abdominal pain/cramps, and diarrhea [63–65].

Prucalopride has been extended out of the licensed indication with encouraging results in treating patients with severe dysmotility, such as an acute form of pseudo-obstruction [66] and chronic intestinal pseudo-obstruction in a patient with Steinert myotonic dystrophy [67]. In the only trial so far published, Emmanuel et al. investigated the effects of prucalopride in a multiple n-of-1 trial based on 7 CIPO patients. Three of them dropped the study because of the complex experimental design. In the 4 CIPO patients (3 with an underlying myopathy and 1 with neuropathy) 2–4 mg daily for 12 weeks of prucalopride significantly improved symptoms such as pain, nausea, vomiting, and bloating, and reduced the use of rescue analgesia in 2 patients. Bowel's habit did not substantially change [68]. Further studies are awaited to test the efficacy of prucalopride and other new 5-HT4 agonists in PIPO/CIPO patients. Finally, it is worth mentioning that prucalopride can reverse the oxidative stress mediated neuronal insult in cultured human enteric neurons, suggesting neuroprotective effects of 5-HT4 agents, which deserve more research in PIPO/CIPO patients with enteric neuropathy [69].

3.1.1.4. Motilin and erythromycin. Motilin is a 22 amino-acid polypeptide synthesized and released by endocrine cells of the GI mucosa [70–72]. Acting through specific receptors, this regulatory peptide evokes phase III contractions of the interdigestive migrating motor complex (MMC) in various species including humans [20]. Notably, plasma motilin levels reach the peak at the end of phase III in the stomach and

duodenum during the interdigestive phase, thereby initiating coordinated motility throughout the GI tract [20]. Based on these results, a number of studies was aimed to identify and develop possible motilin receptor agonists as potential agents for gut motility disorders. In this line, the antibiotic erythromycin exhibited prominent motilin-like effects, eliciting antroduodenal phase III and accelerating gastric emptying [20,73,74]. The effect of erythromycin (or other macrolides) in the distal small intestine and colon has never been established, although they are likely less prominent than in proximal GI tract, since motilin receptors are scarcely expressed in the ileum and colon, as demonstrated in experimental animals [75]. Erythromycin (as well as other motilin agonists) evokes tachyphylaxis resulting from motilin receptor down-regulation, which occurs in about 4 weeks after the beginning of treatment [76,77]. Newly developed erythromycin-derived agonists with no antimicrobial and enhanced motilin-like activities (e.g. mitemcinal) have been generated and broadly termed as 'motilides.' In this paragraph, however, we will cover only erythromycin and related antibiotics as none of the motilides have been used in patients with PIPO/CIPO [78].

A few retrospective case series on the long-term use of erythromycin in CIPO have been published. Emmanuel et al. studied 15 CIPO patients and showed that orally administered erythromycin at dose ranging from 1.5 to 2.0 g/day was effective in 6 cases (n = 3 primary visceral myopathy; n = 2 apparently normal histology; n = 1 scleroderma related visceral myopathy). Compared to non-responders, responders were mainly males (5 out of 6) with an underlying histologically/immunohistochemically proven myopathy, had a significant improvement of symptom profile (i.e. decreased pain and vomiting, normalized bowel function and reduced subobstructive episodes), and used less opioids to control abdominal pain in the long term [79].

Practical aspects include the route of administration and doses. Indeed, a better efficacy in improving symptoms has been demonstrated when erythromycin is administered orally (as ethylsuccinate or estolate) in adult patients [73]. However, oral or intravenous drug administration (as lactobionate) showed similar efficacy in pediatric patients [78]. The suggested dose to achieve efficacy is 3–5 mg/kg per dose in children [1]. In adults, intravenous erythromycin appears to be most effective in acute situations (starting with 3 mg/kg every 8 hours) and continued with oral administration (250 mg 3 times a day) for 5–7 days [1]. The most common side effects of erythromycin include nausea, abdominal pain, bloating, and diarrhea, while intravenously it can cause irritation and thrombophlebitis at the infusion site [1,79]. Furthermore, erythromycin should be cautiously co-administered with agents known to alter or be metabolized by cytochrome P450 (CYP) 3A4 (e.g. diltiazem or verapamil or domperidone) as drug interaction increases the risk for sudden cardiac death [80,81].

Azithromycin (1 mg/kg intravenously) might be an alternative in the treatment of patients with PIPO/CIPO with a better safety profile than erythromycin in children [82,83]. Overall, the use of these drugs in clinical practice depends on accurate evaluation pondering the potential of tachyphylaxis, cardiac risk due to cytochrome interference, and the possible development of antibiotic-dependent bacterial resistance.

3.1.1.5. Other antibiotics with prokinetic effects.

Further to preventing the SIBO development (see below), amoxicillin/clavulanate (20 mg/kg up to antibiotic dose) has been shown to evoke preprandial duodenal phase III, thus resulting in accelerated small bowel transit. Hence, amoxicillin/clavulanate could be used in combination with prokinetic agents [84].

3.1.1.6. Somatostatin and somatostatin analogues.

Somatostatin is a regulatory peptide contained in enteroendocrine (D) cells distributed throughout the GI tract and pancreas as well as in enteric neurons. The two main bioactive forms of somatostatin, consisting of 14 and 28 amino acids, modulate a wide array of GI function via a family of six G protein-coupled receptors [85,86]. Octreotide, the cyclized, long-acting somatostatin analogue, binds preferentially to type 2 receptors. In healthy volunteers, 10 µg of subcutaneous octreotide increased the mean frequency of MMCs in the small intestine, whereas in patients with scleroderma, a condition known to alter the neuromuscular architecture of the gut in about 50% of cases, 100 µg of subcutaneous octreotide evoked MMCs similar to the spontaneous complexes observed in control subjects [87]. Soudha et al. showed that subcutaneous octreotide (50 µg/day for three weeks) was effective in improving GI symptoms (i.e. bloating, abdominal pain, and nausea) and reducing SIBO in 5 patients with scleroderma-related CIPO [88]. Additional studies confirmed the efficacy of octreotide in scleroderma [89–92], as well as in other connective tissue disease-related CIPO [93,94]. Octreotide, in addition to his prokinetic effects, decreases intestinal secretion and lower sensory perception (possibly contributing to reduce pain sensation) [89]. A practical issue pertains to when octreotide should be given. Because gastroparesis is often associated with CIPO [95] and meal ingestion worsens gastroparesis-related symptoms, physicians should recommend octreotide administration during fasting, e.g. during nighttime [88–90,96], or in patients in parenteral nutrition to decompress the gut and decrease SIBO. Octreotide and erythromycin can trigger phase III contractions via different pathways, therefore the synergic effect of these two molecules has been tested in CIPO patients as combination therapy. In the only study so far published, Verne et al. showed that subcutaneous octreotide 50 µg once at bedtime, and oral erythromycin 200 mg 3 times daily resulted in a long term (>8 months) improvement of nausea and abdominal pain in 5 out of 14 (5 with scleroderma and 9 idiopathic) CIPO patients. Notably, patients who were more likely to respond to octreotide and erythromycin were those displaying at least 5 phase III-like motor events over a period of 4 hours after octreotide administration [90]. Finally, clinical improvement using octreotide has also been reported in patients with CIPO associated with malignancies like small-cell lung carcinoma and gastric adenocarcinoma [25,97].

Experience with the use of octreotide in pediatric patients is limited. In a recent retrospective study, octreotide was used in 19 total PN-dependent PIPO patients at a dose of 0.2–1 µg/kg/day divided into two doses (each administered in 50–75 ml of saline solution via a central venous catheter over 60 min). The use of octreotide resulted in an increased tolerance of enteral feeding in 44% of the patients, a feature, which

correlated with octreotide-induced intestinal phase III and a higher median increase in intestinal motility index. Only four patients reported dose-independent side effects while on octreotide, including allergic reaction (rash) (n = 1), hyperglycemia (n = 1), acute cholecystitis with gallstones (n = 1) complicated with pancreatitis (the last two adverse effects required drug discontinuation) and, finally, one patient developed hypertension that responded to octreotide reduction [98].

3.1.2. Treatment of PIPO/CIPO associated manifestations

In this section, we specifically covered SIBO along with the management of abdominal pain, whereas the reader is referred to orthopramides or other serotonin antagonists (i.e. anti-5-HT3 such as ondansetron, tropisetron, and granisetron) for nausea/vomiting.

3.1.2.1. Treatment of SIBO. Although a precise and exhaustive definition cannot be easily established, SIBO is commonly defined as an increased number and abnormal type of microorganisms (mainly bacteria and likely fungi, viruses, and protozoa) colonizing the small bowel [99]. About 30–50% of PIPO/CIPO develop SIBO [99,100]. The main mechanisms can be ascribed to intestinal stasis, resulting from impaired peristalsis, altered/absent phase III of the MMCs, absent/diminished postprandial response, reduced amplitude of antral/intestinal phasic activity and impaired antro-duodenal coordination. The clinical identification of SIBO in PIPO/CIPO patients is difficult since symptoms and signs, such as abdominal pain and distension, bloating, and flatulence often overlap. Also, diarrhea/steatorrhea can occur and contribute significantly to electrolyte abnormalities, key elements (zinc and copper), and vitamins (A, E, D, and B12) deficiencies along with nutrient malabsorption/maldigestion [99–107]. Taken together with all these features, SIBO in the context of PIPO/CIPO has a negative impact on the clinical picture and patient's quality of life [99–107]. Various approaches have been used to objectively detect SIBO, ranging from invasive methods requiring naso-duodenal tube or upper GI endoscopy, i.e. small bowel juice sampling and culture, up to noninvasive breath tests and molecular assays (next-generation, culture-independent microbial analysis) [104–107]. A formal comparison between breath test and small bowel fluid cultures does not exist in PIPO/CIPO; however, a study on patients with unexplained digestive symptoms suggestive of an underlying SIBO showed that duodenal aspiration/culture and glucose breath tests confirmed its presence in 45% and 27% of patients, respectively [104–107]. In the absence of consensus on which method is the gold standard to determine SIBO, small bowel aspirate, and culture appears to be the best approach with its use nowadays limited to research protocols. A bacterial growth $>10^3$ colony-forming units (CFU)/mL of duodenal/jejunal aspirate is the recognized cutoff to establish bacterial overgrowth [99,102,104–107]. As a practical note, the diagnosis of SIBO is based on a) symptoms, clinical signs, and bio-humoral indexes of malabsorption; b) laboratory abnormalities (altered hydrogen/glucose/lactulose breath tests); and, if technically available, c) changes in microbiota composition and numbers [99,104–107].

The management of PIPO/CIPO-related SIBO is challenging, as there is no common agreement concerning the choice, dose, and duration of antibiotic therapy [108,109]. Notably, formal investigations testing different types of antibiotics in PIPO/CIPO-related SIBO are lacking. A meta-analysis by Shah et al. summarized the antibiotics and related doses most commonly used in SIBO treatment, which include amoxicillin/clavulanate (500 mg three times daily), ciprofloxacin (500 mg twice daily), doxycycline (100 mg twice daily), metronidazole (250 mg three times daily), and tetracycline (250 mg four times daily) [108]. Neomycin (500 mg twice daily) and, in particular, rifaximin (550 three times daily in the USA and 400 mg three times daily in Europe) belong to poorly absorbable antibiotics, which reduces the risk of systemic and side effects [108]. Rifaximin can be the antibiotic of choice in SIBO as it shows clinical efficacy (symptom resolution, including abdominal pain), it is virtually non-absorbed in the alimentary canal, induces negligible bacterial resistance, and probably spares some bacterial species of the gut microbiota known to exert beneficial effects (e.g. Lactobacilli). Thus, the term 'eubiotic' has been coined for rifaximin [109–112]. Antibiotics should be administered on a rotation regimen and regardless the type, treatment duration usually lasts 7–10 days up to two weeks per month followed by antibiotic-free periods of variable duration [109–115]. In PIPO cases, possible adverse events or resistance to antibiotics may be controlled by an elemental diet leading to a short-term clinical improvement [116]. Promising data derive from fecal microbiota transplantation (FMT). FMT was administered for 6 consecutive days via naso-jejunal tube in nine patients with CIPO who were followed up for 8 weeks after treatment, showing significant improvements in abdominal bloating and pain two weeks after treatment and resolution of SIBO in 71% (5 out of 7) patients [117].

In conclusion, antibiotic therapy is of paramount importance in patients with PIPO/CIPO-related SIBO in order to reduce symptoms, minimize malabsorption, and improve nutritional status [114,118]. Treatment efficacy can be monitored by symptom amelioration, with duration depending on the severity of dysmotility. Further studies are eagerly awaited to establish the best classes of antibiotics and their clinical and microbiological safety on PIPO/CIPO-related SIBO. Further research is also needed to define the therapeutic potential of FMT in severe gut dysmotility. It is worth mentioning unpublished observations of negative effects of antibiotic therapies in extremely severe CIPO patients, in whom improvement of SIBO-related diarrhea was associated with marked increase of abdominal bloating and pain. This effect requires thorough investigation since diarrhea *per se* might help to control the severity of other digestive symptoms induced by impaired intestinal transit.

3.1.2.2. Analgesics for abdominal pain. The severity of abdominal pain (and other symptoms/signs) in CIPO is worse than that reported in other disorders, including enteric dysmotility and IBS [119]. Thus, chronic abdominal pain is the most disabling symptom experienced by a large proportion of patients with intestinal pseudo-obstruction

syndromes regardless of gender and age [120]. The mechanisms leading to such severe pain remain largely undeciphered, although it is most likely ascribable to various factors, such as bowel distension, spastic contractions (crampy pain crisis), visceral hypersensitivity, and central nervous system activation. In the absence of *ad hoc* trials in PIPO/CIPO, the management of abdominal pain is extremely challenging and empirically based on physicians' experience. According to classic anti-nociceptive strategies, paracetamol is the first-step drug that can be recommended, followed by non-steroidal anti-inflammatory drugs (NSAIDs). As abdominal pain in PIPO/CIPO can be associated to an underlying neuropathy (not necessarily limited to the enteric nervous system), tricyclic antidepressants (TCAs), e.g. amitriptyline, may be used as an alternative to NSAIDs [121]. The analgesic action of TCAs is independent of pain intensity, occurs more rapidly (1–7 days) than the antidepressant effects [122] and its efficacy is well recognized in neuropathic diseases, e.g. diabetes and post-Varicella Zoster infection [123]. However, amitriptyline should be cautiously used at 'low doses' beginning with 10–20 mg/day (which is also in the therapeutic range of pediatric patients) gradually increasing by 10–25 mg every 3–7 days (in adults) being careful to avoid doses ≥75 mg per day likely evoking anticholinergic effects, which worsen gut motility [124]. Other drugs for neuropathic pain may include gamma-aminobutyric acid derivatives, i.e. pregabalin (150–600 mg in twice to three times/day) [125], gabapentin (300–600 mg/day) [126] and duloxetine (a serotonin-norepinephrine reuptake inhibitor). Their role, however, remain to be clarified in severe gut dysmotility. Antispasmodics may be used in PIPO/CIPO patients with predominant crampy pain. However, because of their anti-motility effects, the anti-muscarinic type, namely cimetropium, hyoscine, rociverine, and trimebutine should be avoided, whereas, non-anti-muscarinic antispasmodics (e.g. mebeverine, otilonium and pinaverium) are preferable if deemed clinically necessary [127].

Despite their undisputed efficacy, opioid drugs should be avoided in patients with severe GI dysmotility, especially those with PIPO/CIPO. Indeed, these compounds are known to evoke significant inhibitory effects on motility and secretion via the interaction with receptors widely expressed in the human GI tract [128,129]. Furthermore, opioid drugs are known to evoke dependence in the central nervous system, but not in the GI tract. If a patient with PIPO/CIPO is treated with high-dose opioids, a tapering down strategy up to withdrawal is mandatory to avoid worsening of GI symptoms and pain, the latter likely exacerbated by enteric glia mediated visceral hyperalgesia [130]. Nonetheless, transdermal buprenorphine (a strong opioid acting as partial ι-opioid receptor agonist and a K- and δ-opioid receptor antagonist) has been proposed at a dose of 5 mg/h, which effectively relieved pain in four idiopathic PIPO [131]. Further studies are necessary to know the extent of clinical application of this (and other newly developed) potentially useful opioid drugs [128–131]. Concomitant use of opioid and peripheral μ-opioid receptor antagonists has been demonstrated to prevent constipation without influencing analgesic effects of opioids [129], but it has not been investigated in CIPO/PIPO.

Finally, to our knowledge, only one paper reported the effect of a synthetic cannabinoid (δ-9-tetrahydrocannabinol) in alleviating abdominal pain in a 17-year-old PIPO patient. The analgesic effect may be likely ascribable to a decrease of visceral hypersensitivity [132].

3.1.3. Anti-inflammatory/immunosuppressive treatment for peculiar forms of PIPO/CIPO

The identification of an underlying inflammatory or immune-mediated response, either at tissue level (histologically proven enteric ganglionitis and/or leiomyositis) or by detecting humoral autoimmunity (e.g. circulating anti-neuronal antibodies such as anti-nuclear neuronal antibodies – ANNA-1 or anti-Hu) may justify the use of immune-modifying/anti-inflammatory agents (i.e. steroids, azathioprine, cyclosporine, and methotrexate). Indeed, a number of case reports/small case series indicated the beneficial effects of immune-modifying agents in such patients [133,134]. However, the criteria to define the outcome of immunosuppressive therapy in inflammatory neuro-myopathies have never been established, and the only determinant of a possible positive response is the degree of neuromuscular damage at the time therapy is started (the worst is the pathological damage, the least is the expected pharmacological response). Recently, 'biological agents,' i.e. the monoclonal antibodies targeting cytokines (for example, infliximab, an anti-tumor necrosis factor- α showed clinical and laboratory beneficial effects in two cases with underlying ulcerative colitis [135]. As for most treatments in PIPO/CIPO, also biological agents require formal investigation based on adequate patient selection and well-designed trials. Other options, including plasmapheresis and immunoglobulin treatment are available, but controlled trials to test their efficacy in these patients are still lacking [21,136].

3.2. Nutritional interventions in PIPO/CIPO

These patients often show severe nutritional impairment mainly due to poor intestinal absorption [10,120]. Nutritional interventions, which may be considered as first-line treatment in the management of PIPO/CIPO, are aimed at avoiding protein-energy malnutrition [137,138]. The three main treatment strategies are oral feeding, enteral nutrition (by either bolus or continuous), and PN [6,7,137–142].

3.2.1. Personalized dietary intervention

The management of CIPO patients should include a structured and stepwise approach for an individualized nutritional strategy as highlighted in Figure 2. As an initial step, modifications of oral diet should be performed by a nutritionist and dietician trained in this specific condition. Indeed, since severe digestive symptoms and malabsorption signs affect most patients, the diet should be modulated to guarantee the correct amount and composition of macro- and micro-nutrients, being careful to exclude certain food components that may exacerbate gastrointestinal symptoms (e.g. gas-producing foods – see below). In general, oral feeding should be preferred whenever possible even though small caloric amounts can be consumed. In patients with delayed gastric emptying and adequate bowel absorption, physicians should suggest

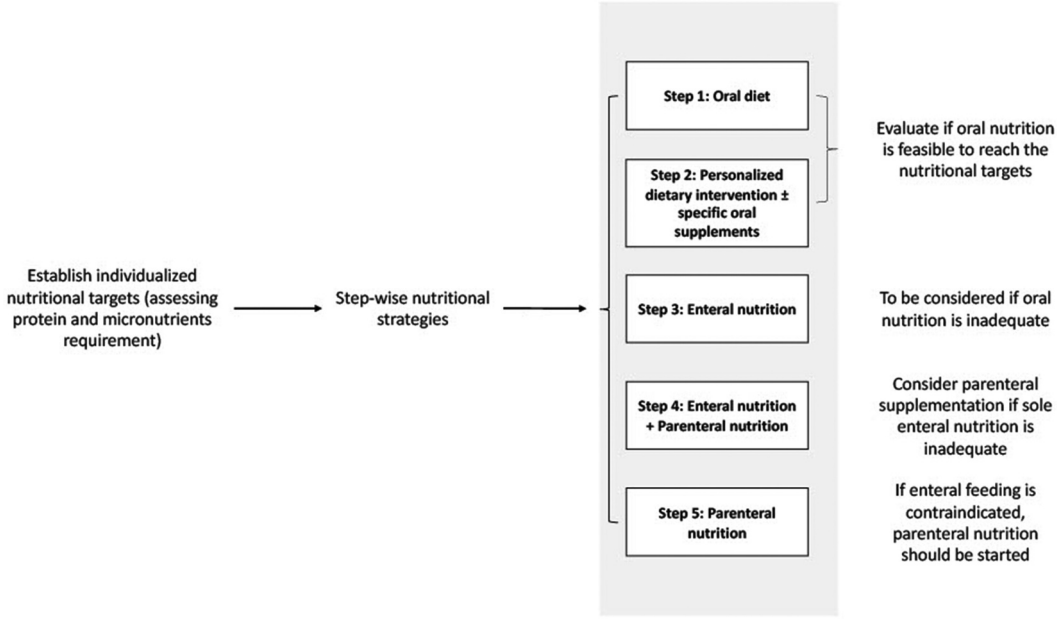

Figure 2. Steps of nutritional interventions in patients with pediatric and adult chronic intestinal pseudo-obstruction.

small and frequent meals (about six times/daily) based on liquid/semi-liquid or soft food [137–143]. A low-lactose, -fructose, -fiber and -fat diet (<30% of fats) should be encouraged in order to avoid worsening of gut motility and decrease the risk of SIBO [10,137–142]. Regarding natural fibers, the hydrophilic ones may be allowed as cooked vegetables (e.g. zucchini, carrots, and potatoes). Moreover, gas-producing foods (ranging from carbonated beverages to brassicaceae, legumes, and milk/milk-derived products) should be avoided [137,138,143–145]. A combined multivitamin and mineral supplementation is recommended [103], including vitamin B12, folic acid, and/or iron (preferably intravenously) especially in patients with SIBO and macrocytic/microcytic anemia. Also, supplementation with vitamin A, D, E, K, and electrolytesin particular, calcium (contributed by lactose-free diet or other nutrient restrictions) may be often required [103]. Finally, an elemental diet (usually composed of amino acids, fats, carbohydrates, vitamins, and minerals) should be integrated with medium-chain triglycerides (e.g. hexanoic acid, 300 mg/day) [10–12,14,145,146]. About one-third of PIPO patients tolerate a modified oral nutrition [1].

3.2.2. Enteral nutrition

Approximately another third of the patients may require intragastric or enteral feeding during the course of the disease [1,142,143]. In patients with an inadequate oral intake or those who are intolerant to oral feeding, an enteral nutrition based on non-elemental (partially hydrolyzed or polymeric) formula should be considered [141,142,146]. This strategy allows for an acceptable daily caloric support and protein intake, which may exert beneficial effect on GI motility and, thereby, enteric absorption [14]. Since elemental-diet is highly osmotic, it may often lead to diarrhea. Thus, in patients with a preserved functional absorptive capacity, the use of elemental diet should not be considered. Enteral nutrition can be added to an oral diet, if necessary.

Different feeding devices can be used at the beginning of artificial nutrition starting with nasogastric tubes. In patients with a delayed gastric emptying, placement of a naso-jejunal feeding tube should be recommended to provide an adequate nutrient support [147–150]. A percutaneous endoscopic gastro-jejunostomy (PEG-J) has been recently indicated as a safe and minimally invasive procedure to improve abdominal symptoms (e.g. bloating and pain) and nutritional status in CIPO patients [14,151,152]. Bolus feeding via PEG-J should not be advised because it may lead to dumping symptoms. Furthermore, PIPO/CIPO patients usually may present delayed gastric emptying and, therefore, enteral nutrition should be modulated (e.g. rate of infusion and/or osmolarity) to avoid complications. Possible failure of enteral feeding may be due to severe enteric dysmotility observed in PIPO/CIPO.

From a practical standpoint, this device is particularly effective as it can be modulated according to symptom fluctuations and its appropriate use (open *vs*. closure intervals) allows for fluid output control avoiding dehydration (which is, in contrast, a common complication of conventional jejunostomy/ileostomy). Enteral nutrition should be administered during the night as a continuous infusion or cyclical bolus feeding [10,11,14,137,138,142]. Compared to boluses of enteral feeding via gastrostomy or jejunostomy, continuous infusion showed a higher long-term efficacy especially in severe PIPO associated with markedly delayed gastric emptying [19,153,154]. In addition to nutritional purposes, PEG-J may be also helpful for venting of air to alleviate bowel distention and symptoms (bloating and pain) [151,152]

However, a long-term tolerance to enteral nutrition cannot be always guaranteed (even in cases with initial improvement) and patients may eventually require PN. If EN is not adequate in terms of caloric intake, PN can be associated [139,148,149].

3.2.3. Parenteral nutrition

Indeed, PN is necessary when oral/enteral nutrition fail to control weight loss and poor nutritional status and/or GI gut dysmotility is so severe to prevent any other feeding strategy [10,14,137–139,148,149]. During the course of CIPO, about 30–50% of patients require PN because of failure of other supportive approaches [10,11,137,138]. In patients with severe, PN-dependent CIPO, the optimum daily caloric intake is 25 kcal/kg/day. Furthermore, about 30% of calories provided by PN should be lipids and another 30% amino acids (1.0–1.5 g/kg/day), while the remaining caloric amount should be covered by dextrose [148,149]. PN may be associated with severe complications, such as liver failure, encephalopathy, pancreatitis, glomerulonephritis, sepsis, metabolic complications (including hyper- or hypo-glycemia), electrolyte disorders, and mechanical catheter obstruction. All these conditions represent frequent causes of morbidity and mortality in PIPO/CIPO [10,11,14,137,138]. The most common complications reported in the literature are hepatobiliary abnormalities (19–75%) and, in the long term, liver failure (up to 50%) [148,149]. The mechanisms leading to liver impairment are likely multifactorial including recurrent catheter-related sepsis, SIBO with bacterial translocation and production of enterotoxins, the latter known to exert a direct hepatocellular damaging effect [99,104]. Compared to other diseases requiring PN, a long-term PN do not increase mortality in CIPO patients [139]. However, severe complications can occur [148,149,155]. Despite the high risk of complications, long-term PN represents a life-saving strategy and, in some clinical conditions (e.g. CIPO refractory to medical treatment), may be considered as a first-line treatment [156,157]. Further research appears necessary to individualize PN formulas and prevent metabolic complications. Mixed-lipid emulsions seem to provide a better balance between omega-3 and omega-6 components; moreover, the presence of anti-oxidants may reduce liver toxicity and cholestasis and likely, the development of intestinal failure associated with liver disease (IFALD) [158,159]. Finally, based on the indications provided by the latest guidelines for PIPO [1] and CIPO [143], an early assessment of nutritional status should be accomplished by a team of clinical nutrition experts via laboratory tests to evaluate intestinal absorptive function and careful appraisal of caloric intake via anthropometric measures (i.e. body mass index and body weight change overtime). Recent evidence indicates that an altered nutritional status in patients with severe chronic gut dysmotility depends on multiple factors [160]. Early management by trained teams, including dieticians, psychologists, and experts in pain therapies is crucial to halt metabolic and nutritional impairment [160]. Moreover, in the absence of effective prokinetics, nutritional support, and fluid/electrolyte supplementation should be considered as key measures in any PIPO or CIPO patient. Furthermore, the management should focus on optimizing oral and enteral nutrition in order to minimize intestinal dysfunction, with PN being a fundamental nutritional approach in selected patients [137,138,142,148,149].

4. Conclusion

PIPO/CIPO is a rare and complex GI motility disorder posing many different challenges; specifically: *i*) wide pathogenetic heterogeneity: a patient with an underlying myopathy may have an identical clinical picture of another whose symptoms/signs can be related to a neuropathy; *ii*) variable natural history and outcomes: some patients develop severe GI symptoms/manifestations abruptly (e.g. as a result of a preceding viral infection), whereas others may show a slow progression to an end-stage disease with massive intestinal dilation and insufficiency; *iii*) patients are often misdiagnosed with other conditions: this causes diagnostic delays, worsening of clinical outcome and quality of life; finally, *iv*) management is largely unsatisfactory, thus significantly increasing frustration in patients, relatives, and physicians. Most, if not all, prokinetic drugs (e.g. ACIs, serotonergic agents, motilides, and others), which should improve/revert GI dysmotility, have been not properly tested in *ad hoc* clinical trials (likely because of the rarity of the disease along with its heterogeneity) and the few available studies did not support their efficacy. Key therapeutic targets are still based on antibiotic therapy for SIBO, control of disabling abdominal pain (possibly avoiding opioids) and nutritional support. Depending on clinical severity of PIPO/CIPO, physicians should ponder carefully the three nutritional options, i.e. oral feeding, enteral, and, in poorly responsive cases (unable to receive an adequate caloric intake) PN. A dedicated team of physicians, dieticians, and nutritional experts is nowadays mandatory to monitor the efficacy of PN and adopt measure aimed at contrasting possible complications such as sepsis and metabolic diseases. If well conducted and followed-up, patients on a PN regimen can be safely maintained with this nutritional measure even in the long term. Taken together, the data presented in this review on pharmacological and nutritional treatment of PIPO/CIPO highlights the current unmet needs in these severe conditions and urge new therapeutic trials for emerging prokinetic drugs as well as *ad hoc* nutritional strategies.

5. Expert opinion

The present article deals with the pharmacological and nutritional management of the 'tip of the iceberg' of all GI motility disorders, namely chronic intestinal pseudo-obstruction in pediatric (PIPO), and adult (CIPO) patients. The evidence so far available indicates that the treatment of this condition does not satisfy patients or physicians. However, in the last five years, there have been significant developments in neurogastroenterology, the discipline investigating research and clinical features of functional and GI motility disorders. These advancements augur well for newly developed (e.g. serotonergic drugs, including naronapride, felcisetrag, and velusetrag) prokinetic agents. From an organizational standpoint, in addition to neurogastroenterologists, a multidisciplinary team including nutritionists/dieticians, radiologists, dedicated nurses, and healthcare providers in tertiary (specialized) referral centers should be involved. Herein we highlighted the unmet needs of PIPO/CIPO treatment. First, any prokinetic

agent should be tested in well designed (double-blind, cross-over), properly balanced (in terms of sample size) clinical trials to establish actual efficacy in patients with PIPO/CIPO. Secondly, a further aspect, which tackles other neurogastroenterological areas, involves the anti-nociceptive strategies to reduce/control visceral pain and abdominal bloating. Notably, both these symptoms often overlap with each other in patients with severe dysmotility. Thus, in addition to pharmacological agents (avoiding opioids) able to limit pain in most functional bowel disorders, other minimally invasive (endoscopic) decompressive measures (PEG-J) should be carefully considered in the management strategy. Decompression of a dilated bowel is aimed at reducing tension of nociceptive nerve endings, thereby minimizing pain generation. Thirdly, SIBO, largely depending on intestinal dysmotility/stasis, contributes to symptoms/clinical signs worsening and nutrient/vitamin deficiency. Thus, managing this condition (by a combination of prokinetic drugs and antibiotics) is a fundamental step in the therapeutic approach of PIPO/CIPO. One of the next challenges will be to implement data on poorly/minimally absorbable antibiotics (e.g. rifaximin) carrying lower risks of bacterial resistance compared to conventional antibiotics. Furthermore, as knowledge on the gut microbiota is expanding, the role of other germs (fungi and viruses) should be investigated in patients with severe dysmotility and hopefully targeted by specific agents if needed. A better understanding of gut dysbiosis will open to novel treatment options including probiotics/symbiotics, postbiotics, genetically engineered bacteria up to FMT, which recent evidence indicates as a promising measure to contrast symptoms as well as gut dysfunction in CIPO and, likely, in PIPO [117,161].

Normal meals cannot be tolerated by virtually all PIPO/CIPO patients as they would contribute to exacerbate disabling symptoms (pain/distension/bloating/nausea and vomiting). Moreover, the severe gut dysmotility hampers significantly the absorption capacity. Thus, a nutritional support, via modified oral feeding and/or enteral nutrition or PN, is a mandatory step to counteract deficiencies (i.e. electrolytes, hydro- or lipophilic vitamins, and oligo-elements), malnutrition, weight loss, and, in the pediatric setting, growth failure. Each patient should be carefully evaluated by a team of nutritionists and dieticians to individualize the best dietary/nutritional strategy. Although never investigated, a reduction of fermentable oligosaccharide, disaccharide, and monosaccharide, and polyols (FODMAPs) may be useful in PIPO/CIPO as it has been beneficial in improving disabling symptoms (bloating and flatulence) in patients with IBS [162]. Further research is needed to clarify the actual effect of a low FODMAPs diet in patients with severe gut dysmotility. Concerning PN, technical (catheters, infusion devices, and timing) advancements along with long-term follow-up are expected to change PIPO/CIPO outcomes. In PIPO/CIPO will be crucial to establish an adequate dietary regimen, supplement the necessary nutrients/substances, while avoiding any possible metabolic abnormalities or other complications should PN be indicated in a long-term basis.

A wide array of results, ranging from newly established molecular targets to cell engineering (i.e. stem cell transplantation to re-build a functional neuromuscular layer of the gut) [163,164] should be viewed as research forefront providing hope for future management of PIPO/CIPO patients. Although research is in progress, significant changes are awaited in the treatment strategies of CIPO thus leading to improved quality and life expectations of such difficult patients.

Abbreviations

ACIs	acetyl cholinesterase inhibitors
ACPO	acute colonic pseudo-obstruction
ANNA	anti-nuclear neuronal antibodies
CIPO	chronic intestinal pseudo-obstruction
EMA	European Medicines Agency
FDA	Food and Drug Administration
FMT	fecal microbiota transplantation
FODMAP	fermentable oligosaccharide, disaccharide, and monosaccharide and polyols
GI	gastrointestinal
hERG	human ether-à-go-go
5-HT	5-hydroxytryptamine
IBS	irritable bowel syndrome
ICC	interstitial cells of Cajal
IFALD	intestinal failure associated liver disease
MMC	motor migrating complex
NSAID	non-steroidal anti-inflammatory drug
PEG-J	percutaneous endoscopic gastro-jejunostomy
PIPO	pediatric intestinal pseudo-obstruction
PN	parenteral nutrition
SIBO	small intestinal bacterial overgrowth
TCA	tricyclic antidepressant

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Data availability statement

There is no data set available for this paper.

Authors' contribution

Conceptualization: GDN, LZ, GB, VS, RDG. Methodology: GDN, LZ, MG, AM, PP. Project administration: GDN, LZ, VS, RDG. Supervision: GDN, LZ, MG, AM, PP, GB, VS, RDG. Writing the original draft: GDN, LZ, AM, PP. Writing/review & editing: MG, GB, VS, RDG. All authors have seen and approved the manuscript and its contents.

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