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SYSTEMATIC REVIEW

Therapeutic Role of Neostigmine and Pyridostigmine in Pediatric Chronic Intestinal Pseudo-Obstruction: A Systematic Review

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Abstract

Background Chronic intestinal pseudo-obstruction (CIPO) is a rare and severe disorder presenting with the clinical and radiological features of intestinal obstruction in the absence of a mechanical cause. When it manifests in children, it is referred to as pediatric intestinal pseudo-obstruction (PIPO). Diagnosis remains challenging and is largely based on exclusion. Management is primarily symptomatic, and among the available therapeutic approaches, cholinesterase inhibitors have emerged as potential options for severe gastrointestinal dysmotility, particularly when conventional treatments are insufficient. This review summarizes the current evidence on the use of pyridostigmine and neostigmine in CIPO, with a focus on pediatric patients.

Methods A systematic review was performed using PubMed, Embase, Web of Science, and Scopus, including all studies published up to July 2025 that evaluated the use of pyridostigmine and neostigmine in pediatric patients with CIPO.

Results Our review identified 22 publications reporting a total of 54 patients. Overall, treatment with neostigmine or pyridostigmine was associated with a favorable clinical response in approximately two-thirds of cases, ranging from partial improvement to complete symptoms resolution. Safety outcomes were generally reassuring, with few adverse events and only rare cases requiring treatment discontinuation.

Discussion Pyridostigmine and neostigmine may represent therapeutic options for pediatric CIPO, with neostigmine appearing particularly effective in acute settings and pyridostigmine more suited to chronic management. Although current evidence supports both safety and potential efficacy, robust clinical trials are essential before these agents can be integrated into standard care protocols.

Key Points

Chronic intestinal pseudo-obstruction (CIPO) is a rare and severe disorder of intestinal motility.

Pyridostigmine and neostigmine demonstrated clinical efficacy in relieving CIPO symptoms.

Both agents may represent therapeutic options for pediatric CIPO.

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1 Introduction

1.1 Chronic Intestinal Pseudo-Obstruction (CIPO)

Chronic intestinal pseudo-obstruction (CIPO) is a rare and severe disorder characterized by clinical and radiological features of intestinal obstruction in the absence of a mechanical cause, moreover, it is also defined as pediatric intestinal pseudo-obstruction (PIPO) when occurring in children [1]. To meet the diagnostic criteria for chronicity, symptoms must persist for more than 2 months in newborns and more than 6 months in older children [2]. The exact incidence is unknown; however, it is estimated to be less than 1 in 40,000, possibly less than 1 in 100,000 [1]. CIPO is generally classified into primary, secondary, and idiopathic forms. Primary CIPO results from intrinsic neuromuscular abnormalities of the gastrointestinal tract and can be histologically categorized into neuropathies, myopathies, or mesenchymopathies, though mixed patterns may occur. Secondary CIPO is associated with a wide range of systemic conditions, including connective tissue diseases, endocrine disorders, neurological diseases,

paraneoplastic syndromes, infections, infiltrative diseases, and metabolic disturbances. Moreover, exogenous causes, such as drug effects, post-surgery complications, and post-transplant side effects have been reported. When no underlying cause is identified despite thorough investigation, the condition is considered idiopathic. Although familial and inherited forms have been described, they remain rare compared with the idiopathic group [3].

Diagnosis is challenging and primarily relies on clinical symptoms, including, abdominal distension, vomiting, abdominal pain, reduced bowel movement, and persistent constipation. Abdominal imaging should be used as routine first screening approach and typically shows bowel distension without evident obstruction. Due to its rarity and the often nonspecific nature of symptoms, it is not uncommon for the diagnosis to be made primarily by exclusion, and some patients may remain undiagnosed [1].

1.2 Therapeutic Approach

The clinical burden of CIPO and the limited efficacy of standard prokinetic agents, such as metoclopramide and serotonergic agents, underscore the need for novel therapeutic approaches [4]. Due to their prokinetic properties, cholinesterase inhibitors have emerged as a potential therapeutic option in selected cases of severe gastrointestinal dysmotility, especially when conventional treatments are insufficient. Pyridostigmine, a long-acting, orally available reversible cholinesterase inhibitor, increases acetylcholine concentrations at the neuromuscular junction within the enteric nervous system, thereby enhancing intestinal motility and promoting coordinated peristalsis [5]. Recent clinical reports in pediatric populations have showed potential efficacy of the treatment with observed outcomes, including reduced abdominal distension, decreased reliance on parenteral nutrition, and improved tolerance of enteral feeding [5, 6]. In adults, pyridostigmine has demonstrated efficacy in the management of CIPO [7], whereas in pediatric patients, available data are still limited and mostly derived from case reports and small case series. Neostigmine has been successfully used as a pharmacologic agent for colonic decompression in acute colonic pseudo-obstruction, with efficacy demonstrated in adult and pediatric cases [4].

Nevertheless, safety considerations remain critical. Available tolerability data are primarily derived from patients treated for myasthenia gravis. The most frequently reported adverse effects are gastrointestinal in nature, including flatulence, abdominal cramps, and diarrhea. Other common side effects include excessive sweating, salivation, and urinary urgency. However, treatment discontinuation due to adverse effects is relatively uncommon and typically occurs in response to severe diarrhea or muscle fasciculations [8].

1.3 Aim of the Review

This review provides an overview of current evidence on the use of pyridostigmine and neostigmine in CIPO, with a focus on pediatric patients. We summarize available clinical data and highlight their potential benefits, safety, and limitations in managing severe gastrointestinal dysmotility.

2 Methods

2.1 Search Strategy

We conducted a systematic literature review on the use of pyridostigmine and neostigmine on CIPO pediatric patients in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9].

A literature search was conducted in PubMed (https://pubmed.ncbi.nlm.nih.gov), Web of Science (https://www.webofscience.com), Embase (https://www.embase.com), and Scopus (https://www.scopus.com) up to July 2025, independently by three authors (L.Z., C.C., and V.R.).

The search strategy included the following key terms: "pyridostigmine" or "neostigmine", and "obstruction", "intestinal", and age-related terms "pediatric", "infant", "children", "adolescent" (Supplementary Table 1).

Inclusion criteria:

- Pediatric patients under 18 years of age.
- Use of pyridostigmine or neostigmine or both.
- Diagnosis of intestinal pseudo-obstruction (regardless of the underlying condition) defined as the presence of clinical and/or radiological features of intestinal obstruction in the absence of a mechanical cause.

Exclusion criteria:

- Adult patients.
- Use of pharmacological agents other than neostigmine or pyridostigmine.

Discrepancies were resolved by consensus among three authors (L.Z., C.C., and V.R.).

2.2 Quality of Study

The quality of the included studies and their associated risk of bias were assessed using the JBI tools for case report and case series studies [10, 11].

3 Results

A total of 275 articles were identified through searches in the 4 databases. After manual screening of titles and abstracts, and removal of duplicates, 22 articles were ultimately selected [5, 6, 12–31].

The workflow of the search was showed in Fig. 1, while summary of the articles was presented in Table 1.

Seven works were conducted in the USA, three in Korea, three in Canada, two in Turkey, three in Italy, and one each in the UK, Spain, Mexico, and Australia.

All included articles were case reports or small case series (1–10 patients), comprising a total of 54 patients (30 male and 24 female, mean age 8.03 ± 5.60 years, range 2 months–21 years).

Various underlying conditions were reported; 7 patients were classified as having primary CIPO, 15 had oncological diseases, 7 underwent abdominal transplant surgery, 3 underwent orthopedic surgery, 11 had genetic disorders, and 11 had other conditions (Table 2). Patients with CIPO without comorbidities were most frequently treated with pyridostigmine, whereas oncological patients were more often treated with neostigmine.

Notably, among the 54 patients, 13 developed CIPO following chemotherapy and 13 after surgery (Table 3). Neostigmine was the only drug administered in cases where CIPO occurred after chemotherapy, and it was also more commonly used in patients who developed CIPO following surgery.

The main symptoms reported included abdominal and intestinal loop distension, constipation, vomiting, abdominal pain, and reduced or absent bowel movements.

The diagnosis was mainly based on the radiological findings of the abdomen, showing bowel distention without mechanical obstruction; however, in a few articles

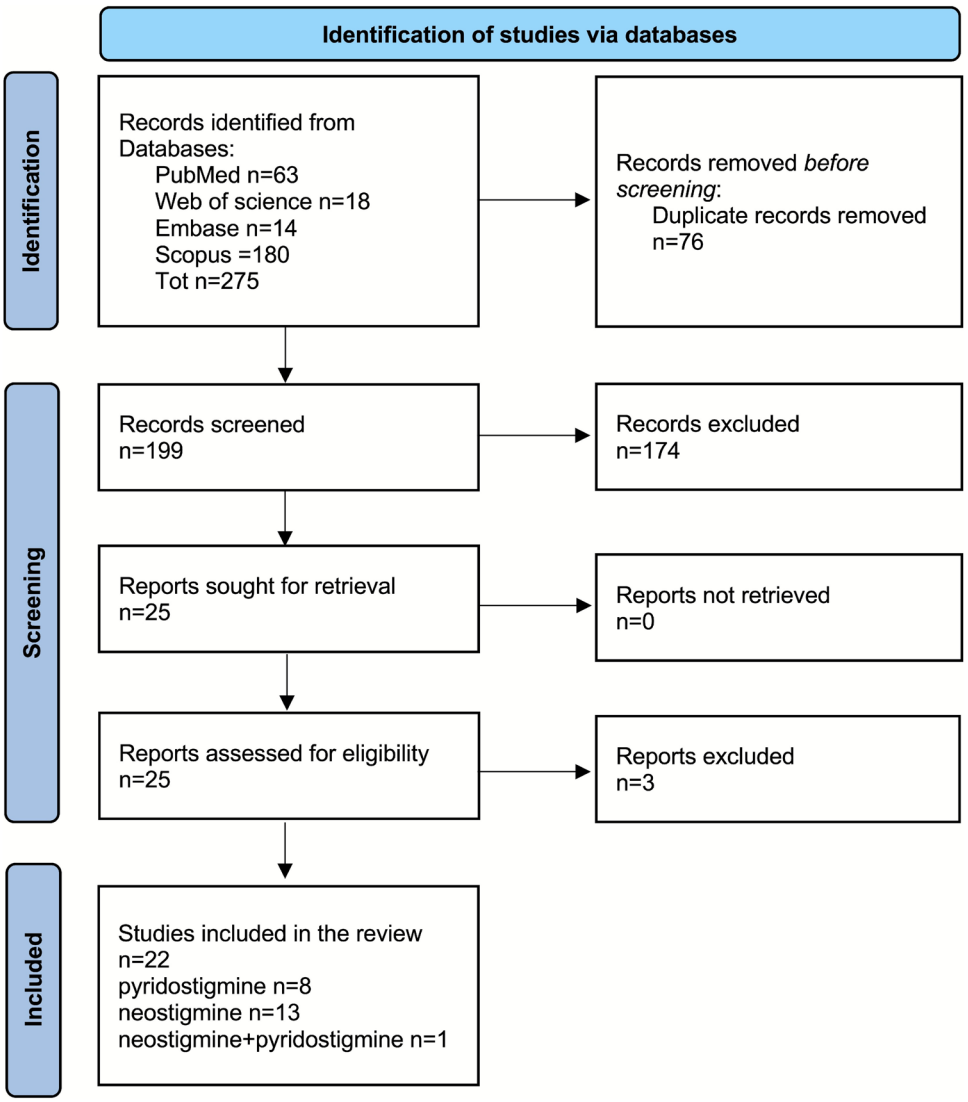

Fig. 1 Workflow of the study identification

Table 1 Summary of clinical characteristics, treatment, and outcomes of pediatric patients with CIPO treated with cholinesterase inhibitors reported in the literature

Authors Nation Reference	Age Sex	Underlying condition	Symptoms	Doses	Outcome	Side effect
Pyridostigmine						
Boybeyi 2009 Turkey 19480337 [12]	3 years M	Megacysts and microcolon	Intermittent intestinal obstruction, probably due to enteric nervous system alteration, micturition difficulties	30 mg/kg/day in the acute phase. Then, continuous treatment for 6 months at 120 mg/day	Decrement of nasogastric decompression, return to oral feeding, normal defecation	None
Capriati 2025 Italy https://doi.org/10.1002/jpn3.70171 [31]	6 years M	Visceral myopathy	Very high score on gastrointestinal Symptom Rating Scale questionnaire regarding all GI symptoms, CIPO	Highest dosage 1.6 mg/kg/day, total 575 days	≥ 25% increase in enteral/oral feeding energy	None
	10 years M	Neurogenic CIPO	Very high score on gastrointestinal Symptom Rating Scale questionnaire regarding all GI symptoms, CIPO	Highest dosage 3.4 mg/kg/day, total 820 days	No improvement	None
	12.8 years F	*ACTG2* visceral myopathy	Very high score on gastrointestinal Symptom Rating Scale questionnaire regarding all GI symptoms, CIPO	Highest dosage 3.1 mg/kg/day, total 1825 days	≥ 25% increase in enteral/oral feeding energy, reduction in the number of hospitalizations	None
	9 years F	*ACTG2* visceral myopathy	Very high score on gastrointestinal Symptom Rating Scale questionnaire regarding all GI symptoms, CIPO	Highest dosage 2 mg/kg/day, total 150 days	≥ 25% increase in enteral/oral feeding energy	Bradycardia
	5.5 years M	Neurogenic CIPO	Very high score on gastrointestinal Symptom Rating Scale questionnaire regarding all GI symptoms, CIPO	Highest dosage 2 mg/kg/day, total 850 days	≥ 25% increase in enteral/oral feeding energy	None
	21.5 years M	Cerebral palsy	Very high score on gastrointestinal Symptom Rating Scale questionnaire regarding all GI symptoms, CIPO	Highest dosage 0.44 mg/kg/day, total 1284 days	≥ 25% increase in enteral/oral feeding energy, reduction in the number of hospitalizations	None
	8 years M	*ACTG2* visceral myopathy	Very high score on gastrointestinal Symptom Rating Scale questionnaire regarding all GI symptoms, CIPO	Highest dosage 0.73 mg/kg/day, total 120 days	≥ 25% increase in enteral/oral feeding energy	None

Table 1 (continued)

Authors Nation Reference	Age Sex	Underlying condition	Symptoms	Doses	Outcome	Side effect
	10 years F	Mitochondrial disease WARS2 genetic variant	Very high score on gastrointestinal Symptom Rating Scale questionnaire regarding all GI symptoms, CIPO	Highest dosage 2.9 mg/kg/day, total 365 days	No improvement, reduction in the number of hospitalizations	None
	5 years F	*ACTG2* visceral myopathy	Very high score on gastrointestinal Symptom Rating Scale questionnaire regarding all GI symptoms, CIPO	Highest dosage 1 mg/kg/day, total 180 days	No improvement, reduction in the number of hospitalizations	None
	5.33 years F	Spinal muscular atrophy type 1	Very high score on gastrointestinal Symptom Rating Scale questionnaire regarding all GI symptoms, CIPO	Highest dosage 1.6 mg/kg/day, total 120 days	≥ 25% increase in enteral/oral feeding energy, reduction in the number of hospitalizations	None
Choudhury 2018 UK 10.1542/ peds.2017-0007 [5]	9 years F	Congenital myotonic dystrophy	Intermittent abdominal distension and constipation, urinary involvement	From 0.5 to 1 mg/kg twice per day enteral after 7 months 1.5 mg/kg, total 12 months	Improvement of clinical symptoms, reduction of abdominal distension, return to oral nutrition intake	Not reported
Comisi 2024 Italy https://doi.org/10.3389/fped.2024.1460658 [13]	10 years M	Alpha-thalassemia X-linked intellectual disability (ATR-X) syndrome	Chronic gastroesophageal reflux, severe persistent constipation, gastroparesis, and severe intestinal loop distension	Oral dose of 30 mg/day (1.6 mg/kg/day) increased to 60 mg/day (3.2 mg/kg/day) within 20 days. Maintenance dose oral 45 mg/day 1 year	After a year of treatment, gastrointestinal symptoms resolved, with no recurrence of abdominal distension or fecal stasis	No significant side effects
Dahiya 2021 USA https://doi.org/10.1177/23247096211034303 [14]	18 years F	Medical history of migraine headaches Hollow visceral myopathy	Severe gastroparesis, chronic intestinal, pseudo-obstruction	No dose reported	No clinical improvement, isolated small intestine transplant improves the symptoms	Not reported
Di Nardo 2019 Italy https://doi.org/10.5056/jnm19078 [6]	2 years F	Long-term history of constipation, food refusal, and low weight and height gain	Vomiting, diarrhea, constipation	From 2 mg/kg to 3 mg/kg twice a day, 3 days	After 3 days improvement of the symptoms, development of spontaneous bowel movements, reduction of abdominal distension, disappearance of vomiting, and tolerance of oral feeding	Not reported

Table 1 (continued)

Authors Nation Reference	Age Sex	Underlying condition	Symptoms	Doses	Outcome	Side effect
Manini 2018 USA https://doi.org/10.1007/s40272-017-0277-6 [15]	18 years M	Chronic constipation and gastroesophageal reflux, mid-gut volvulus CIPO	Post-surgery CIPO worsening, abdominal distension, gastrostomy, ileostomy,	0.25 mg/kg/day two doses than 0.3 mg/kg/day 2 years	Improvement of abdominal distension, increment of enteral calories	None
	7 years F	Developmental delays, cortical blindness, and hearing loss	Abdominal distension, constipation, vomiting	10 mg orally four times daily (4 mg/kg/day) then 10 mg orally twice daily (2 mg/kg/day) 3 months	Improvement of abdominal distension, bowel movement, vomiting resolution	None
	11 years F	Pelvic sarcoma	Post-surgery sigmoid colostomy Abdominal distension, pain, vomiting	30 mg three times daily (1.7 mg/kg/day) then 30 mg twice daily (1.1 mg/kg/day) at least 72 h	First improvement within 24 h, improvement of abdominal distension, pain, and vomiting Interruption of the treatment after 72 h due to side effects	Abdominal pain and cramps
	10 years F	Vesicourethral reflux, ureteral implantation	Abdominal distension, pain, vomiting	1.1 mg/kg/day then 2.2 mg/kg/day 6 months	Improvement of abdominal distension, vomiting, minimal change in pain	None
Turer 2019 Turkey https://doi.org/10.5152/tjg.2020.19233 [17]	20 months F	CIPO	Constipation abdominal distention, vomiting	0.25 mg/kg/day	Partial response (improvement in oral intake and obstructive symptoms) Subjected to ileostomy exitus due to sepsis	Not reported
	2 months F	CIPO	Constipation, abdominal distention, vomiting	0.25 mg/kg/day, at least 3 weeks	Absence of improvement in oral intake and obstructive symptoms after therapy lasting at least 3 weeks Subjected to ileostomy, stoma	Not reported
	2 months F	CIPO	Constipation, abdominal distention, micturition difficulty	0.25 mg/kg/day	Partial response (improvement in oral intake and obstructive symptoms) Subjected to ileostomy	Not reported

Table 1 (continued)

Authors Nation Reference	Age Sex	Underlying condition	Symptoms	Doses	Outcome	Side effect
	3.5 years F	CIPO	Constipation abdominal distention, vomiting, diarrhea	0.25 mg/kg/day	Partial response (improvement in oral intake and obstructive symptoms) Subjected to ileostomy, stoma, bridectomy	Not reported
	6 months M	CIPO	Constipation abdominal distention, micturition difficulty	0.25 mg/kg/day	Partial response (improvement in oral intake and obstructive symptoms)	Not reported
	5 years M	CIPO	Abdominal pain, constipation, abdominal distention	0.25 mg/kg/day	Partial response (improvement in oral intake and obstructive symptoms)	Not reported
Neostigmine						
Althausen 2001 USA https://doi.org/10.1097/00002517-200112000-00014 [18]	17 years M	Orthopedic spinal patient	Postoperative ileus, acute abdominal distension and abdominal pain	Single dose 2 mg intravenously	Improvement in 5.25 min, range 3–10 min Evacuation of flatus or stool, significant reduction in abdominal distension and discomfort	Excessive salivation
Brar 2025 Canada https://doi.org/10.1016/j.jpainsymman.2025.04.019 [19]	94 days M	Severe hypoxic ischemic encephalopathy	Pediatric intestinal pseudo-obstruction, reduced bowel movement, abdominal distension	Single subcutaneous dose 0.01 mg/kg at 100 days of life, second dose at 105 days of life	Increment of bowel movements, resolution of abdominal distension, and resumption of oral feeds in 6 days	Mild emesis after 15 min
Garcia 2018 Canada PMC6146187 [20]	17 years F	Neuromuscular scoliosis secondary to CP and spastic quadriparesis	After orthopedic surgery, abdominal pain and distension Septic shock	Oral dose not reported	Condition worsened, cecal perforation, treatment interruption Successfully treated with surgery	Not reported
Gmora 2002 Canada https://doi.org/10.1053/jpsu.2002.35438 [21]	4 years M	Spastic quadriplegia, severe developmental delay	After orthopedic surgery progressive abdominal distension and obstipation Acute colonic pseudo-obstruction	Intravenously initial dose of 0.1 mg (0.007 mg/kg) up to total dose of 0.75 mg (0.05 mg/kg) over 5 h	First improvement within 3.5 h Complete clinical resolution of the pseudo-obstruction after 1 day, relaxation of abdomen, defecation	Not reported

Table 1 (continued)

Authors Nation Reference	Age Sex	Underlying condition	Symptoms	Doses	Outcome	Side effect
Gonzalez 2011 Spain https://doi.org/10.1097/MPG.0b013e3182187bab [22]	4 years M	Fontain surgery for hypoplastic left heart syndrome	Post-surgery constipation, abdominal distension	Intravenous 11 µg/kg/h 12 h	Increased intestinal peristalsis Increase in bowel sounds, passage of gas, abundant bowel movement Resolution in 12 h	None
	7 years M	Fontain surgery for hypoplastic left heart syndrome	Post-surgery abdominal sepsis Refractory constipation	Continuos intravenous, maximum doses 5 µg/kg/h 18 h	First improvement 2 h Elimination of fecal material Resolution of refractory constipation	None
	17 years M	Heart transplant	Post-surgery abdominal distension, no bowel movement	Intravenous maximum dose of 11 µg/kg/h 30 h	No response, infusion was discontinued after 30 h Situation resolved 2 days later with increased dose of polyethylene glycol (max 2 g/kg/day)	Not reported
Hooten 2014 USA USA10.3171/2014.6.PEDS13636 [23]	15 years F	Scoliosis	After orthopedic surgery, abdominal pain nausea, colonic dilation	Single administration, 0.04 mg/kg dose	Improvement in abdominal pain and distension after 10 min After 12 h, reduced colonic distension After 1 week, normal bowel function	Not reported
Jessop 2010 Australia https://doi.org/10.1111/j.1440-1754.2010.01906.x [24]	12 years M	Childhood acute lymphoblastic leukemia	Post-chemotherapy acute colonic pseudo-obstruction	Intravenous initial dose of 0.1 mg, incremental doses of 0.05 mg every 20 min (0.05 mg/kg maximum dose) up to 48 h	Complete improvement of symptoms within 48 h	Not reported
	12 years F	Childhood acute lymphoblastic leukemia	Post-chemotherapy acute colonic pseudo-obstruction	Intravenous initial dose of 0.1 mg, incremental doses of 0.05 mg every 20 min (0.05 mg/kg maximum dose)	Successful return of gastrointestinal motility exitus after septicemia	Not reported
Johnson 2012 USA USA10.1089/jpm.2011.0450 [25]	14 years F	Multifocal small cell osteosarcoma	Increased abdominal distension, abdominal pain, constipation	Intravenous single dose 2 mg	Mild decrease in abdominal distension Interruption of the treatment due to side effects Ileostomy	Diffuse erythema, sensation of throat closure, and dyspnea

Table 1 (continued)

Authors Nation Reference	Age Sex	Underlying condition	Symptoms	Doses	Outcome	Side effect
Khosla 2008 USA https://doi.org/10.1016/j.jpedsurg.2008.07.030 [26]	3 years F	Sickle cell disease	Pain at leg, arm, chest, abdomen Vomiting, difficulty breathing, acute colonic pseudo-obstruction	Intravenous 0.15 mg (10 µg/kg), once per day for 2 days	Within 6 h large bowel movements After 3 days the symptom greatly improved, reduction of abdominal distension at day 7 discharged from hospital	Not reported
Kim 2007 Korea https://doi.org/10.1097/MPH.0b013e318063ef4b [27]	9 years M	Cerebellar medulloblastoma, seizure	Vomiting, constipation After chemotherapy, acute colonic pseudo-obstruction, abdominal distension, vomiting	Subcutaneously 0.25 mg (0.01 mg/kg/dose) 3 times at 12-h intervals 36 h total	Vomiting disappeared after 12 h, defecation, decreased distension and rigidity	Not reported
Lee 2010 Korea https://doi.org/10.5045/kjh.2010.45.1.62 [28]	Median age 8.5 (range 3–14) years 8M, 2F	8 acute lymphoblastic leukemia 1 malignant lymphoma 1 juvenile myelomonocytic leukemia	After chemotherapy, acute colonic pseudo-obstruction	Subcutaneously at 0.01 mg/kg/dose (maximum, 0.5 mg/dose) twice daily, maximum 5 doses	Half of the patients: improvement of clinical symptoms after 1 day (2 doses) Median range time to response 29 (range 1–70) h. Response rate 80% (8/10). 1 patient: symptom improvement after 105 h, 1 patient: symptom improvement after 77 h	$n = 1$ diplopia $n = 1$ aggravated abdominal pain
Mier Escurra 2016 Mexico https://doi.org/10.1016/j.bmhimx.2016.04.003 [16]	13 years M	Delayed psychomotor development due to perinatal asphyxia kidney transplant	Post-surgery abdominal pain, distended abdomen Acute colonic pseudo-obstruction	3 doses 1.5 mg of neostigmine	Reduced abdominal distension Further clinical improvement	Not reported
Petersen 2019 USA https://doi.org/10.1111/petr.13564 [29]	12 years M	Orthotopic liver transplantation due to Wilson disease	Severe refractory postoperative ileus, Distended air-filled, bowel loops	Intravenous initial 0.007 mg/kg/h titrated up by 0.001 mg/kg/h to effect maximum dose 0.009 mg/kg/h 2 h and 40 min	Bowel movement within 2 h 1 day ileus resolution	Intermittent abdominal cramping during infusion

Table 1 (continued)

Authors Nation Reference	Age Sex	Underlying condition	Symptoms	Doses	Outcome	Side effect
	9 months M	Hepatoblastoma orthotopic liver transplantation	Severe postoperative ileus	intravenous 0.008 mg/kg/h, titrated up to 0.016 mg/kg/h over 5 h after 4 more h, dose increased by 0.004 mg/kg/h and subsequently increased by 0.004 mg/kg/h every h maximum dose 0.05 mg/kg/h 19 h	After 1 h 10 min first improvements After 1 day clinical resolution of the ileus	None
	3 years M	Acute liver failure, orthotopic liver transplantation	Post-surgery generalized bowel distention secondary to severe ileus, severe refractory ileus	Intravenous four bolus start and max 0.012 mg/kg/h One bolus start 0.005 mg/kg/h max 0.009 mg/kg/h, total 88.5 h of infusion	First improvement after 10 h after fifth infusion (88.5 h) Bowel sounds normoactive with flatus and stooling resolution of ileus, bowel decompression	None
Neostigmine + pyridostigmine						
Lee 2019 Korea https://doi.org/10.1097/MPG.0000000000002183 [30]	5 years F	*ACTG2* genetic variant -enteric smooth muscle actin	CIPO	Intravenous neostigmine 0.5 mg at 0.5 mg/h for 1 h. From dose 0.5 to 2.5 mg/day After 10 days oral pyridostigmine 180 mg/day	Reduction of hospital length of stay and parenteral nutrition Outcome related to CIPO not reported	Not reported
	11 years F	*ACTG2* genetic variant-enteric smooth muscle actin	CIPO	Intravenous neostigmine 0.5 mg at 0.5 mg/h for 1 h. From dose 0.025 mg/kg/day to 0.04 mg/kg/day After 10 days oral pyridostigmine 7 mg/kg/day	Reduction of hospital length of stay and parenteral nutrition Outcome related to CIPO not reported	Not reported

CIPO chronic intestinal pseudo-obstruction; *CP* cerebral palsy; *F* female; *GI* gastrointestinal; *M* male

the authors did not report the imaging findings for all the patients described [15, 22, 29, 30].

In 1 article, neostigmine and pyridostigmine were administered subsequentially [30], 13 works used neostigmine alone [16, 18–28, 32], and 7 used pyridostigmine alone [5, 6, 12–15, 17].

Neostigmine was primarily administered intravenously or subcutaneously. Pyridostigmine was administered orally in two patients, however, most of the studies did not report the route of administration (Table 4).

Effective pyridostigmine doses varied from 1 to 4 mg/kg/day for acute treatment and from 0.44 to 3.1 mg/kg/day for chronic therapy lasting months to years. Lower dosage (0.25 mg/kg/day) generally resulted in only partial effects. In a single case, a higher dose of 30 mg/kg/day was administered and was associated with symptomatic improvement. For acute management, neostigmine was effective at a subcutaneous dose of 0.01 mg/kg (for 1–3 doses). When administered as a continuous intravenous infusion, effective maximum doses were 0.005–0.011 mg/kg/h for approximately 1 day; in one case, a maximum dose of 0.05 mg/kg/h was reported (Table 1).

The duration of the treatment ranged from a single dose of pyridostigmine to more than 3 years of treatment, while neostigmine was administered for periods ranging from short intravenous infusion to 10 days. Symptom resolution was achieved in 36 cases (overall rate 66.7%, 56% when pyridostigmine was used, 81% when neostigmine was used), while in 7 cases improvement was partial (13%) and in 9 cases the therapy was ineffective (16.7%) (Table 5).

The reported outcomes used to define successful treatment included improvement of clinical symptoms, reduction of abdominal distension and pain, normalization of bowel movement and defecation, resolution of vomiting, increased tolerance or intake of oral feeding, and decreased hospitalization. Outcomes were defined as partial by the authors when there was no complete resolution of symptoms but only some ameliorations.

Nevertheless, pyridostigmine was not effective in an 18-year-old patient with no prior medical history, whose symptoms resolved only after an isolated small intestine transplant [14], and in a 2-month-old infant with CIPO onset at 3 days of life [17]. Moreover, it was not efficacious in a case of neurogenic CIPO, in a patient with *ACTG2* related visceral myopathy, and in a child with mitochondrial disease [31]. Neostigmine was ineffective in a patient with cerebral palsy and spastic quadriparesis who developed CIPO after scoliosis surgery and was later subjected to an ileocecal resection due to a cecal perforation [20], in a heart-transplant patient whose symptoms resolved after 2 days with polyethylene glycol administration [22], and in two oncologic patients [28]. In the study where neostigmine and pyridostigmine were administered sequentially, the authors reported a shortening in the hospital length of stay and parenteral nutrition use, but did not describe the exact impact of the treatment on gastrointestinal symptoms [30].

When the patients were categorized according to the myopathic or neurogenic nature of their disorders, the success rates were lower with myopathic CIPO in respect to those with neurogenic CIPO. In the case where CIPO was nonspecific, symptom resolution was achieved in three out of eight patients (Table 6).

Few side effects were reported, and those described were generally mild, including abdominal pain, cramps, vomiting, salivation, diplopia, and bradycardia. In one case, diffuse erythema, a sensation of throat closure, and dyspnea following neostigmine infusion led to discontinuation of the treatment [25]. In another case, abdominal pain and cramps after pyridostigmine administration resulted in treatment discontinuation (Table 7) [15].

When assessing the risk of bias with the JBI tools, which are appropriately tailored for case reports and case series, most items were rated as low risk (Supplementary Table 2). However, it is important to consider that case series and case reports inherently presented potential biases due to their observational design and the absence of control arm.

4 Discussion

This review summarizes the available evidence on the use of pyridostigmine and neostigmine in the management of CIPO in pediatrics.

While both drugs are well-known acetylcholinesterase inhibitors with established efficacy in several conditions, their application in CIPO remains off-label and supported mainly by anecdotal reports, small case series, and heterogeneous patient populations.

Our analysis identified 22 publications reporting on a total of 54 patients. Overall, treatment with neostigmine or pyridostigmine was associated with a favorable clinical response in two-thirds of cases, ranging from partial improvement to complete resolution of symptoms. Neostigmine, typically administered intravenously or subcutaneously, had a rapid onset of action and higher rates of symptom relief, particularly in acute colonic pseudo-obstruction and postoperative ileus. In contrast, pyridostigmine, mostly given orally, more frequently employed in patients with chronic or recurrent symptoms, showed slower onset but it was associated with sustained improvement in gastrointestinal function in selected cases. Notably, in some cases pyridostigmine treatment was continued for several months or even years. These observations suggest that the two agents may have complementary roles: neostigmine as an acute rescue therapy, and pyridostigmine as a maintenance treatment for chronic dysmotility. The heterogeneity of underlying conditions,

Table 2 Therapeutic applications of neostigmine and pyridostigmine in reviewed literature

Condition	All $n = 54$	Pyridostigmine $n = 25$	Neostigmine $n = 27$	Neostigmine + pyridostigmine $n = 2$
Chronic intestinal pseudo-obstruction	7 (13%)	7 (28%)	0 (0%)	
Genetic disorder	11 (20%)	8 (32%)	1 (4%)	2 (100%)
Oncological condition	15 (28%)	1 (4%)	14 (52%)	
Transplant surgery	7 (13%)	0 (0%)	7 (26%)	
Orthopedic surgery	3 (6%)	0 (0%)	3 (11%)	
Other	11 (20%)	9 (36%)	2 (7%)	

Table 3 Underlying conditions of CIPO in reviewed literature

Possible cause of CIPO symptoms	All $n = 54$	Pyridostigmine $n = 25$	Neostigmine $n = 27$	Neostigmine + pyridostigmine $n = 2$
Post-surgery	13 (24%)	2 (8%)	11 (41%)	
Post-chemotherapy	13 (24%)	0 (0%)	13 (48%)	
Other	28 (52%)	23 (92%)	3 (11%)	2 (100%)

Table 4 Documented administration routes for neostigmine and pyridostigmine in reviewed literature

Route of administration	Total $n = 56$	Pyridostigmine $n = 25$	Neostigmine $n = 27$	Pyridostigmine + neostigmine
Intravenous	12 (22%)	0 (0%)	12 (44.4%)	
Subcutaneous	12 (22%)	0 (0%)	12 (44.4%)	
Oral	3 (6%)	2 (8%)	1 (3.7%)	
Enteral	1 (2%)	1 (4%)	0 (0%)	
Intravenous + oral	2 (4%)	0 (0%)	0 (0%)	2 (100%)
Not reported	24 (44%)	22 (88%)	2 (7.4%)	

Values are rounded; therefore, percentages may not total exactly 100%

Table 5 Therapeutic outcomes and response rates to neostigmine and pridostigmine treatment

Successful outcome	All $n = 54$	Pyridostigmine $n = 25$	Neostigmine $n = 27$	Neostigmine + pyridostigmine $n = 2$
Yes	36 (66.7%)	14 (56%)	22 (81%)	
No	9 (16.7%)	5 (20%)	4 (15%)	
Partial	7 (13%)	6 (24%)	1 (4%)	
GI result not reported	2 (3.7%)	0 (0%)	0 (0%)	2 (100%)

GI gastrointestinal

Values are rounded; therefore, percentages may not total exactly 100%

including oncological diseases, transplant-related complications, genetic disorders, and idiopathic CIPO, substantially complicates the interpretation of treatment outcomes. Nevertheless, the relatively higher efficacy observed with neostigmine in post-surgical and chemotherapy-related pseudo-obstruction highlights its possible utility in acute

secondary forms, while pyridostigmine appears more effective in primary or idiopathic CIPO. Importantly, though only one of the reviewed studies reported this approach, the combination or sequential use of both drugs may represent an area for future investigation.

Children with severe neurological impairment (SNI) represent a subgroup of relevance. In these patients, complex gastrointestinal dysfunction is increasingly recognized and has recently been framed under the concept of gastrointestinal dystonia (GID), a syndrome characterized by severe feed-related symptoms, hypertonicity, abdominal distension, and distress, often leading to malnutrition and reliance on long-term parenteral nutrition [33, 34]. In this vulnerable population, therapeutic strategies are frequently limited by polypharmacy and high procedural risk, making pharmacological agents with motility-enhancing properties, such as pyridostigmine and neostigmine, an attractive option. While current evidence remains scarce, their use could potentially alleviate feed intolerance and reduce symptom burden when treatment is carefully individualized and integrated within a holistic care plan including nutritional, neurological, and palliative perspectives.

Safety outcomes were generally reassuring, with few adverse events and only rare cases requiring discontinuation of therapy. Reported side effects were mostly mild and self-limiting, including abdominal cramps, salivation, and transient emesis.

Beyond the heterogeneous causes of CIPO, there are several other limitations of our research. First, all available studies are case reports or small series, with inherent risk of bias and lack of standardized outcome measures. Moreover, there is an intrinsic reporting bias, as negative results are likely to be underreported; indeed, cases in which the treatment was unsuccessful are less frequently described and published. Second, dosing regimens, routes of administration, and treatment durations varied widely, precluding the definition of clear evidence-based protocols. Neostigmine was typically administered for short periods or as single bolus doses and was effective at subcutaneous dose of 0.01 mg/kg. When it was administered in continuous intravenous infusion, it was effective at maximum doses of 0.005–0.011 mg/kg/h for approximately 1 day. Pyridostigmine was used both in acute and maintenance phases, with efficacious oral doses ranging from 1 to 4 mg/kg/day for acute treatment and 0.44–3.1 mg/kg/day for chronic therapy, which could last months or years; in contrast, only partial effects were reported at lower dosages (0.25 mg/kg/day). Third, most studies lacked long-term follow-up, making it difficult to assess the durability of clinical benefits or the impact on quality of life and nutritional autonomy.

Future research should prioritize prospective, multicenter studies aimed at defining optimal dosing strategies, identifying predictors of treatment response, and evaluating long-term safety. The development of standardized clinical

Table 6 Therapeutic efficacy of acetylcholinesterase inhibitors in myopathic and neurogenic chronic intestinal pseudo-obstruction

Successful outcome	Myopathic $n = 11$	Neurogenic $n = 35$	Not specific $n = 8$
Yes	6 (55%)	27 (77%)	3 (37.5%)
No	3 (27%)	5 (14%)	1 (12.5%)
Partial	0 (0%)	3 (9%)	4 (50%)
GI result not reported	2 (18%)	0 (0%)	0 (0%)

GI gastrointestinal

Table 7 Side effects associated with neostigmine and pyridostigmine treatment

Side effects	All $n = 54$	Pyridostigmine $n = 25$	Neostigmine $n = 27$	Neostigmine + pyridostigmine $n = 2$
Not reported	15 (28%)	9 (36%)	6 (22%)	
None	31 (57%)	14 (56%)	15 (55%)	2 (100%)
Abdominal pain and cramps	1 (2%)	1 (4%)		
Excessive salivation	1 (2%)		1 (4%)	
Mild emesis	1 (2%)		1 (4%)	
Diffuse erythema, sensation of throat closure, and dyspnea	1 (2%)		1 (4%)	
Diplopia	1 (2%)		1 (4%)	
Abdominal pain	1 (2%)		1 (4%)	
Abdominal cramping	1 (2%)		1 (4%)	
Bradycardia	1 (2%)	1 (4%)		

Values are rounded; therefore, percentages may not total exactly 100%

endpoints and patient-reported outcomes would be crucial to strengthen the evidence base. Furthermore, translational research exploring the pathophysiology of enteric neuropathies and the mechanisms of response to cholinesterase inhibitors may help tailor treatment to specific patient subgroups.

In conclusion, pyridostigmine and neostigmine may be considered as therapeutic options for pediatric CIPO, with neostigmine showing particular benefit in acute settings and pyridostigmine in chronic management. While current evidence supports their safety and potential efficacy, robust clinical trials are needed before these agents can be integrated into standard therapeutic protocols.

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Declarations

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