Chronic Intestinal Pseudoobstruction

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Opinion statement

Patients with chronic intestinal pseudoobstruction (CIP) experience a constellation of symptoms including abdominal pain, nausea, fullness, and malaise which fluctuates in severity and invariably result in a diminished quality of life. Though surgical resection or transplantation may be an option for some, there currently is no cure for CIP. Thus, management strategies utilize pharmacologic, intravenous, endoscopic, and surgical techniques to promote transit, minimize painful bloating, reduce complications of stasis, and improve quality of life. Prokinetic agents such as erythromycin, metoclopramide, cisapride, neostigmine, and tegaserod may be effective for acute exacerbations. Octreotide may reduce symptoms of bacterial overgrowth and bloating by stimulating migrating motor complexes. Enteral tubes for venting and nutritional support may reduce hospitalizations. Total parenteral nutrition (TPN), fraught with well-known complications, may be the only tolerated source for nutrients and fluid. Advanced disease may magnify nutritional problems, difficulties of long term intravenous and intestinal access, and poor symptom control. Because the initial process may manifest in other intestinal regions following surgery, resection of involved segments should be performed with caution. Small intestinal transplantation is a high-risk surgery performed in persons unable to tolerate intravenous (IV) nutrition. Optimal management for persons with CIP should not only provide nutritional and symptom focused care but should be part of a supportive network which links patients to their appropriate healthcare needs.

Introduction

Chronic intestinal pseudoobstruction (CIP) is a rare intestinal motility disorder that manifests as episodes of intestinal obstruction without mucosal or structural evidence of mechanical blockage. Symptoms vary depending on the location of involved segments, duration and severity of the disease. Focal sites within the small intestine and colon are most common but the esophagus, stomach, even the ureter and urinary bladder can be involved.

ETIOLOGY

CIP results from injury to the neural control mechanisms responsible for intestinal peristalsis. In health, food is propelled through the intestinal tract as a result of the synchronized contraction and relaxation of intestinal segments. Peristalsis occurs through the complex trafficking of signals from the intrinsic neural network of the gut (including the interstitial cells of Cajal [ICC]), to the extrinsic nervous system emanating from the brain and spinal cord, and finally to the intestinal smooth muscle. CIP can develop if one or more of these systems are impaired. The ICC, known as the pacemaker cells of the gut, form a plexus within the intestinal wall that are often reduced in number or absent in patients with pseudoobstruction [1,2].

Primary familial or sporadic visceral neuromuscular disorders are uncommon causes of CIP. Pseudoobstruction is most often secondary to conditions that impair neuromuscular function (Table 1). Narcotic use is a par-

Table 1. Causes of chronic intestinal pseudoobstruction

Primary chronic intestinal pseudoobstruction
Visceral myopathy (familial or sporadic)
Visceral neuropathy (familial or sporadic)
Normal histology variant (sporadic only)
Secondary chronic intestinal pseudoobstruction
Drugs
Narcotics
Antidepressants
Anticholinergics
Parkinson's medications
Clonidine
Vincristine
Phenothiazines
Endocrine disorders
Diabetes mellitus
Hypo- or hyperthyroidism
Hypoparathyroidism
Infections
Chagas disease
Cytomegalovirus
Epstein-Barr virus
HIV
Muscle disorders
Scleroderma
Systemic lupus erythematosus
Dermatomyositis
Amyloidosis
Myotonic dystrophy
Progressive or Duchenne muscular dystrophy
Neurologic disorders
Diabetic neuropathy
Parkinson's disease
Dysautonomia
Malignancy affecting neural structures
Multiple sclerosis
Amyloidosis
Paraneoplastic syndromes
Scleroderma

ticularly common cause of 'reversible' pseudoobstruction. Opiates act by blocking smooth muscle contraction and thus impair peristalsis. Medications that interfere with neurotransmitter signaling, or systemic disorders (*eg*, diabetes, scleroderma, infections) that damage cells critical to the relay of signal or stimulation of muscle contraction can lead to stasis and symptoms of obstruction. Small cell lung cancer and carcinoid tumors can cause immune-mediated paraneoplastic CIP [3]. The antineuronal nuclear antibody (anti-hu) shares an epitope with the malignancy and intestinal neuronal elements [4]. Primary or metastatic tumors may encase neural structures leading to CIP.

CLINICAL FEATURES

The clinical features of CIP are dependent on many factors, including duration and severity of illness, segment length, number of organs involved, co-morbidities, and degree of nutritional compromise. Early in disease, symptoms are generally mild, intermittent, and may be assumed to be due to a gastrointestinal (GI) infection. Persistent delay in transit, stasis, development of nutritional deficiencies, and weight loss may develop with disease progression. There is often a chronic and acute component to CIP. Chronic phase patients may experience sensations of low grade fullness, bloating, nausea, and pain. Severe, acute exacerbations occur at irregular intervals, and frequently without identifiable triggers. Exacerbations are often preceded by a short prodrome of malaise, followed by abrupt onset of incapacitating nausea, cramping pain, and persistent retching that may require hospitalization and IV fluid resuscitation. Bowel evacuation patterns become irregular in advanced disease with a predilection to difficult to manage constipation. Diarrhea or steatorrhea may be caused by overgrowth of bacteria in stagnant segments of intestine. Impaired transit with segmental stasis leads to poor absorption of nutrients and eventual weight loss. Successful nutrition management via enteral feeding tubes may become compromised if disease begins in segments beyond the catheter tip. Finally, clinical depression may accompany GI symptoms if a subject's enjoyment of food and quality of life are continually challenged.

DIAGNOSIS

A diagnosis of CIP is based upon a history of recurrent GI symptoms with features of intestinal obstruction and without evidence of mechanical blockage. Early in disease, GI symptoms may include mild abdominal fullness, intermittent nausea, and a change in bowel pattern, usually constipation. With disease progression, signs of delayed transit, stasis, and gradual development of nutritional deficiencies or weight loss may predominate. Severe, acute exacerbations of nausea, vomiting and dehydration are indicative of mechanical blockage or pseudoobstruction; the importance of excluding blockage is obvious as obstruction is cured with surgical intervention.

The history should address potentially reversible causes of delayed transit such as medication use, metabolic disorders, travel, or infection history as well as any family history of neuromuscular problems (Table 1). Discontinuing offending medications or treating infectious or metabolic disorders is appropriate before proceeding with an extensive evaluation (Table 2). Narcotic pain medications are a common cause of delayed intestinal transit and CIP-like symptoms. Narcotic bowel syndrome, a disorder characterized by worsening abdominal pain, constipation, and transit delay in the face of escalating doses of opiates [5] is treated by discontinuation of opiates, including synthetic preparations. Detailing onset

Table 2. Overview of the evaluation and treatment of pseudoobstruction

Evaluation
Exclude medications and treatable metabolic disorders as cause of symptoms
Plain radiography and contrast studies to rule out mechanical obstruction
Transit tests and esophageal manometry to evaluate motility
Evaluate nutritional status
Gastroduodenal manometry to assess for neuropathic/myopathic process
Colon manometry if evaluating for focal disease
Consider laparoscopy to obtain full thickness biopsy for diagnosis
Treatment
Chronic maintenance
Cisapride
Octreotide
Metoclopramide
Tegaserod
Endoscopically or surgically placed tube for venting
Endoscopically or surgically placed tube for enteral nutrition
Total parenteral nutrition
Resection of affected segments
Intestinal transplantation
Acute exacerbations
Intravenous erythromycin
Metoclopramide
Tegaserod
Neostigmine
Surgical intervention
Associated diarrhea/steatorrhea
Rotating schedule of antibiotics for small bowel bacterial overgrowth
Octreotide nightly to decrease the likelihood of bacterial overgrowth

of symptoms of aspiration, dysphagia, early satiety, nausea, bloating, or a change in bowel habits began may suggest an inciting trigger such as a stroke, infection, injury, or medication. If involvement of other organ systems are suspected by symptom complaints (*eg*, extremity weakness, shortness of breath, blurry vision) selected scans or labs tests may identify a condition to account for all symptoms.

Laboratory studies should include serum glucose, thyroid-stimulating hormone, complete blood count with differential, albumin, and vitamin B12. Selective tests of rheumatologic disease such as ANA, sedimentation rate, and rheumatoid factor may be in order. Consider tissue confirmation of antibodies, autoantigens or vasculitis if selective rheumatologic tests are positive.

Excluding obstruction is paramount. Plain films of the abdomen, contrast radiographs of the upper and lower GI tract are indicated; computed tomography (CT) scans and endoscopic examinations should be performed if these are negative. If symptoms of aspiration, difficulty swallowing, early satiety, or change in bowel habit are present use of specialized tests that examine these segments is appropriate. Videoflouroscopy or a pharyngoesophagram will identify subtle aspiration or a swallowing disorder that may be missed by esophagram. Esophageal manometry will exclude a motor disorder. Gastric, small intestine, and colon transit tests may indicate selective organ involvement or reduced overall transit. If colon transit is abnormal, outlet obstruction can be excluded by anorectal manometry and balloon expulsion. Colon manometry can identify the presence of abnormal motility patterns not identified by other tests. If the patient has a positive smoke history, a chest CT may be considered to exclude a small cell lung cancer, a cause of paraneoplastic intestinal dysmotility. An immunofluorescence assay of the antineuronal nuclear antibody (anti-hu) may be positive even in the absence of detectable cancer.

If small bowel involvement is suspected but the etiology remains unclear a gastroduodenal manometry in the fasting and fed state can confirm a diagnosis of a neuropathic or myopathic process (Fig. 1). This test is not available at most centers but can be useful to confirm a diagnosis of pseudoobstruction. Neuropathies characteristically exhibit uncoordinated, variable amplitude contractions throughout the small bowel. Myopathies are characterized by low amplitude pressure activity (<20 mm Hg) in the proximal small bowel and may be associated with concomitant bladder dysfunction.

Suspected brain or spinal cord lesions (*eg*, multiple sclerosis (MS), tumors) can be screened by CT or magnetic resonance imaging scans (MRIs). Performing laparoscopic surgery for tissue biopsies of an involved segment may establish a diagnosis but is associated with some risk and rarely alters medical management, therefore it is often avoided. Biopsies can be obtained at the time of surgical placement of enteral tubes.

Laparoscopy for focal resection and or tissue diagnosis should be performed only if there is clear evidence that the disease is limited (*eg*, megaduodenum, slow transit constipation) or if the diagnosis will alter management.

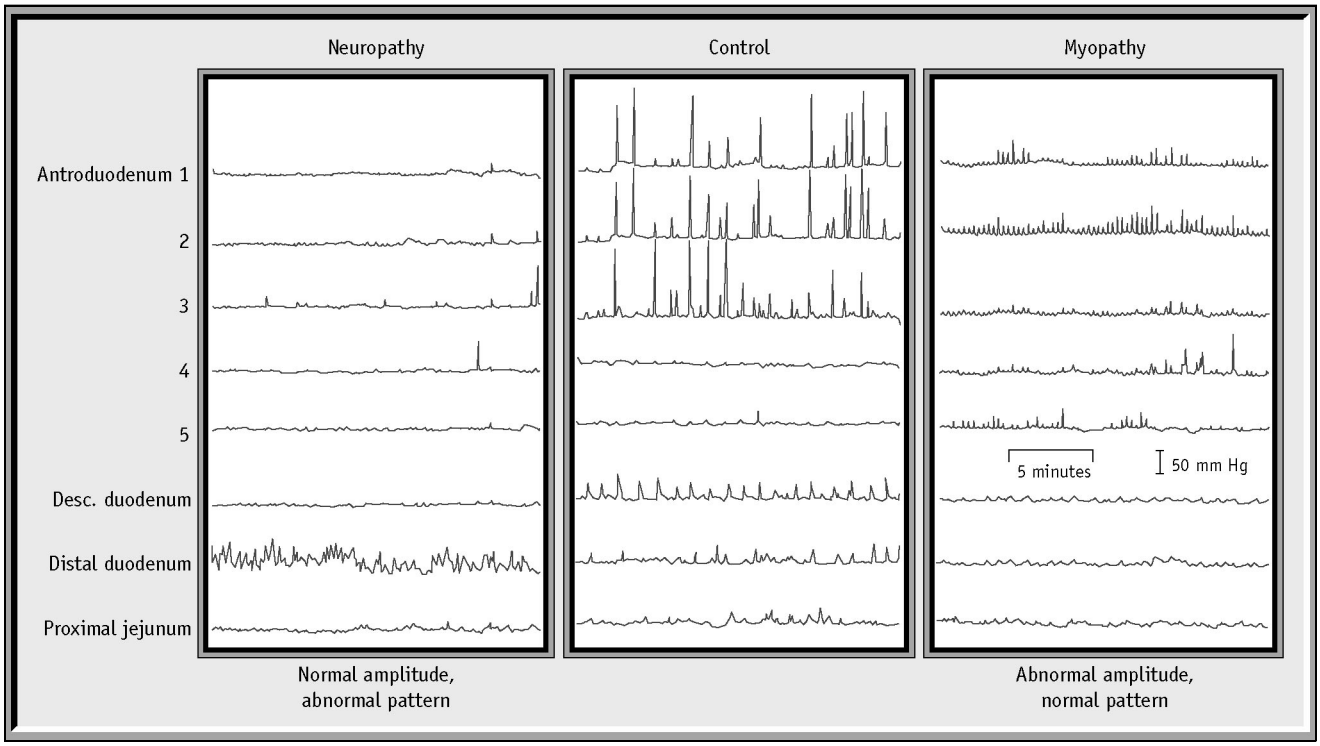

Figure 1. Gastroduodenal manometry. Fed patterns of intestinal motility in normal control, neuropathic and myopathic causes of pseudoobstruction.

Treatment

Diet and lifestyle

- Maintaining sufficient oral intake can be the primary difficulty in treating patients with chronic intestinal pseudoobstruction. Low lactose, low fat, and low residue diets have been proposed [6] as a means of reducing abdominal symptoms. Vitamin levels, especially the fat-soluble vitamins A, D, E, and K, and water soluble B12 should be monitored and supplemented as needed.
- Patients unable to maintain sufficient oral intake, and who develop dehydration and malnutrition may require supplemental or total parenteral nutrition [7]. Total parenteral nutrition (TPN) may be a means of providing fluid and caloric intake, and may be crucial to symptom control. For many patients ingestion either orally or via feeding tubes can produce severe abdominal symptoms that can be avoided by parenteral administration. In combination with decompression tubes, TPN can be used for symptomatic relief.
- Although total parenteral nutrition allows patients to maintain hydration and caloric intake, complications related to TPN are the most common cause of death in children with chronic intestinal pseudoobstruction [8].

Pharmacologic treatment

- Pharmacologic treatment in chronic intestinal pseudoobstruction is primarily aimed at promoting intestinal motility. Increased motility may enable patients to maintain a sufficient enteral intake to maintain nutritional needs and can decrease the symptoms associated with abdominal distention.
- Pharmacologic treatment with antibiotics in chronic intestinal pseudoobstruction may reduce the overgrowth of bacteria associated with small intestinal stasis.

Erythromycin

	IV Erythromycin use has also been reported to be effective during acute exacerbations of chronic intestinal pseudoobstruction and may produce some temporary symptomatic improvement; chronic oral erythromycin has not been effective in the treatment of pseudoobstruction due to a side-effect of secondary to tachyphylaxis [9,10].
Standard dosage	500 mg IV every eight hours for exacerbations of chronic intestinal pseudoobstruction.
Contraindications	Sensitivity to Erythromycin, liver disease, concomitant use of Cisapride, cardiac arrhythmias.
Main drug interactions	Cisapride, digoxin, coumadin.
Main side effects	Cardiac arrhythmias, QTc prolongation, headache, abdominal pain, cramping, nausea and vomiting, diarrhea, cholestatic jaundice, increased liver function tests.
Special points	May be helpful during acute exacerbations but not for chronic treatment.
Cost effectiveness	One month of erythromycin is approximately $40.

Metoclopramide

	A trial of metoclopramide may be used for symptoms of chronic intestinal pseudoobstruction. However, a double-blind, placebo-controlled trial using 10mg Metoclopramide four times daily, however, did not demonstrate a difference from placebo in symptom control [11].
Standard dosage	10 mg four times daily.
Contraindications	Sensitivity to or Extrapyramidal effects from metoclopramide.
Main drug interactions	Phenothiazines, Lithium, Antiepileptics.
Main side effects	Extrapyramidal effects.
Special points	Randomized trial shows no difference from placebo.
Cost effectiveness	One month of metoclopramide is $40.

Octreotide

	In uncontrolled studies, octreotide 100 μg per day was shown to induce migrating motor complexes, and to improve measures of bacterial overgrowth and abdominal symptoms in chronic intestinal pseudoobstruction [12]. Controlled trials of octreotide in CIP are unavailable.
Standard dosage	50 to100 μg subcutaneously at bedtime.
Contraindications	Sensitivity to octreotide or any components of injection.
Main drug interactions	Patients receiving insulin, oral hypoglycemic agents may require dosage adjustments of these agents.
Main side effects	Pain at injection site, headaches, dizziness, and hypo/hyperglycemia.
Special points	Administered once nightly, octreotide may provide symptomatic relief from abdominal distention and may reduce bacterial overgrowth by inducing migrating motor complexes. Although expensive, octreotide may be cost effective by providing a promotility effect and by decreasing the need for rotating antibiotics.
Cost	Nightly use of octreotide from a multidose bottle costs about $600 per month.

Cisapride

	Cisapride is a serotonin-4 receptor agonist which increases GI motility. This agent was removed from the market in the year 2000 by the US Food and Drug Administration (FDA) because of deaths related to cardiac arrhythmias. It is available for patients who meet specific clinical criteria. In the setting of CIP it has been shown to stimulate duodenal contraction [13,14], but in double blinded placebo controlled studies 10 mg three times daily was not effective. Patients with manometric evidence of migrating motor complexes (MMCs) at baseline, with no significant dilation of bowel and no evidence of vagal neuropathy may be the most likely to benefit [15•,16]. A dosage of 20 mg three times daily may be effective, but controlled trials at this dosage are not available [16].

Standard dosage	20 mg three times daily.
Contraindications	Sensitivity to cisapride, family or personal history of cardiac arrhythmias, prolonged QTc interval, use of medications that inhibit CYP3A4, use of potassium wasting diuretics, renal failure.
Main drug interactions	Many drugs cause increased cisapride blood levels and interact with cisapride to prolong the cardiac output interval. A careful review of patient's medication profile is required.
Main side effects	Cardiac arrhythmias, death.
Special points	May be most effective in patients without bowel dilation and without evidence of vagal neuropathy. Requires special clearance for use.
Cost effectiveness	Cisapride taken three times daily will cost $140 per month.

Tegaserod

	Tegaserod, an agonist for 5HT4 serotonin receptors, has been FDA approved for constipation-predominant irritable bowel syndrome in women [17,18]. Use of tegaserod in chronic intestinal pseudoobstruction has not yet been reported. Given evidence that it promotes gastric emptying and small intestinal transit in addition to improving colonic transit [19, 20], this medication may prove useful in patients with CIP, especially given the potential for diffuse involvement of the GI tract in patients with pseudoobstruction.
Standard dosage	2 or 6 mg two times daily .
Contraindications	Bowel obstruction or adhesions, liver or renal failure, suspected sphincter of Oddi dysfunction.
Main drug interactions	None reported
Main side effects	Diarrhea
Special points	May hold promise in CIP given its promotility effects in stomach, small bowel, and colon.
Cost effectiveness	One month of tegaserod costs $150.

Neostigmine

	Neostigmine is an acetylcholinesterase inhibitor administered intravenously. Neostigmine has been shown in controlled trials to reduce cecal diameter quickly in the setting of acute colonic pseudoobstruction. Chronic use of IV neostigmine in acute exacerbations of chronic intestinal pseudoobstruction has been performed by the authors, but no controlled clinical trials have been performed to determine safety, and this agent may be useful in exacerbations of CIP. Controlled trials of neostigmine in chronic intestinal pseudoobstruction are unavailable.
Standard dosage	0.2 to 2.0 mg IV as required up to every six hours.
Contraindications	Sensitivity to Neostigmine, cardiac arrhythmias.
Main drug interactions	Increased risk of bradycardia with beta-blockers, calcium channel blockers or digoxin.
Main side effects	Bradycardia, nausea, vomiting, abdominal cramping
Special points	Effective in acute colonic pseudoobstruction. Reported in chronic pseudoobstruction. Must be administered in a monitored setting due to the cardiac effects.
Cost effectiveness	A single dose of IV neostigmine will cost about $1, but associated costs of administration and monitoring make the costs much higher.

Antibiotics

	Chronic Intestinal Pseudoobstruction can be complicated by bacterial overgrowth in stagnant segments resulting in diarrhea and steatorrhea. Testing with breath tests or duodenal aspirates may not be reliable in diagnosing bacterial overgrowth as stasis may occur in more distal segments. Therefore, the empiric use of antibiotics in CIP complicated by diarrhea has been advocated [6]. Typically one-week courses are adequate with a rotating schedule of two or three, a few antibiotics are given in a rotating schedule to reduce the likelihood of developing antibiotic resistance.
Standard dosage	Ciprofloxacin 500 mg two times daily. Doxycycline 100 mg two times daily. Metronidazole 250 mg three times daily or amoxicillin/clavulanic acid 125 to 500 mg twice daily for seven to 10 days of each month.

Contraindications Sensitivity to antibiotics.
Main drug interactions Warfarin, cisapride.
Main side effects Allergic reactions.
Special points Typically a single agent is given seven to 10 days of each month with a drug-free interval. Multiple agents are given in a rotation to decrease likelihood of developing resistant organisms.
Cost effectiveness A one week course of ciprofloxacin costs about $70. Amoxicillin/clavulanic acid costs $90 a week. Less expensive options include one week of doxycycline $25 and metronidazole $10.

Endoscopic therapy

- Endoscopic gastrostomy or jejunostomy tubes may be used for the purpose of decompression.
- Endoscopic tubes may also be used to provide enteral nutrition in some settings.
- In the setting of chronic colonic pseudoobstruction, an endoscopic cecostomy tube can provide a permanent means of colonic decompression.

Percutaneous endoscopic gastrostomy or jejunostomy

A percutaneous endoscopic gastrostomy (PEG) tube may be placed for gastric venting. A dual channel gastrostomy with an extension of one port into the jejunum may allow venting via the gastric port and enteral nutrition via the jejunal port. A direct jejunostomy (PEJ) may allow for more distal access for decompression or enteral access.
Standard procedure Upper endoscopy or extended upper endoscopy with percutaneous tube placement.
Relative contraindications Previous abdominal surgery.
Complications Perforation, bleeding, infection of tube site.
Special points These tubes are more likely to be successful as a means of decompression of the stomach or proximal small intestine. For the tube to be useful in providing nutritional supplementation, jejunostomy tubes must be placed distal to affected segments. Surgically placed jejunostomy tubes allow for more distal access.

Surgery

- Surgical management of chronic intestinal pseudoobstruction provides the ability to resect regions of localized disease.
- Surgery to place gastrostomy and enterostomy tubes provide for venting and nutritional access.
- Intestinal transplantation has been described in children with chronic intestinal pseudoobstruction.

Bowel resection or bypass

Resection or bypass of diseased segments and even subtotal enterectomy has been used in CIP [21,22••]. If localized diseased segments can be identified, resection of these segments may provide symptomatic relief and enable the patient to return to enteral nutrition [23]. Subtotal enterectomy may be required for symptomatic relief in the setting of diffuse disease. Parenteral nutrition is required for the consequent short-bowel patient.
Standard procedure Resection of diseased segments.
Contraindications Patients unfit for surgery.
Complications Hemorrhage, infection, and occurrence of disease in remaining segments.

Special points Surgical resection allows for full thickness biopsies for diagnostic purposes. Patients may require near total enterectomy for symptomatic control of markedly dilated segments and thus require parenteral nutrition.

Decompression or feeding tube placement

Surgical gastrostomy, enterostomy, or cecostomy tube placement can provide symptomatic relief via decompression and has been demonstrated to reduce hospitalization rates in CIP [22••,24].

Standard procedure If endoscopic placement of PEG is not available or if surgical exploration is required, a surgically placed gastrostomy or jejunostomy tube can be used for feeding or venting.

Contraindications Patients unfit for surgery

Complications Hemorrhage and infection.

Special points Surgical placement of feeding tubes may provide better access to distal nondiseased segments of intestine beyond the reach of standard or extended endoscopes.

Ileostomy or colostomy

Performing a surgical placement of a standard ileostomy or colostomy procedure could result in diversion of the intestinal stream proximal to diseased egments, offering a menas decompression [23].

Standard procedure Ileostomy or colostomy with or without colectomy.

Contraindications Patients unfit for surgery.

Complications Bleeding and infection.

Special points Effective for patients with CIP restricted to the colon or distal ileum and colon.

Intestinal Transplantation

Intestinal transplantation is a high-risk procedure to be considered in patients with severe CIP. It has been suggested that only patients who cannot receive adequate nutritional support through TPN, or individuals in whom intravenous access cannot be maintained, or those who have had TPN related liver damage should be considered candidates considered for intestinal transplantation. In the setting of coexistent liver disease, a combined liver and small intestinal transplant would be performed [25•].

Standard procedure Small bowel transplantation or combined small bowel and liver transplant.

Contraindications Patients unfit for surgery.

Complications Immediate complications of surgery. High rate of rejection and graft-versus-host-disease compared to other transplant patients. Toxicity from immunosuppressants. Greater than half of patients still require enteral or parenteral feeding supplementation [24].

Special points Intestinal transplantation may be best undertaken in children where a potential cure is offered for an often fatal condition.

Emerging therapies

- Electrical stimulation has been used in the setting of gastroparesis with equivocal results. Theoretically, the small intestine could be stimulated extrinsically by application of surface electrodes, however, the length of the organ and difficulty in coordination of contractile activity make intestinal pacing an unlikely intervention to occur in the near future. Thus far no reports have been published on pacing in chronic intestinal pseudoobstruction.
- The combination of a 5-HT4 agonist and opioid antagonist has been shown to be effective in enhancing intestinal propulsion in in vitro studies. Clinical trials are needed to evaluate efficacy in GI motility disorders [26••].

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