Review Article

Recommendations for Bowel Obstruction With Peritoneal Carcinomatosis

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Abstract

This article reports on the clinical practice guidelines developed by a multidisciplinary group working on the indications and uses of the various available treatment options for relieving intestinal obstruction or its symptoms in patients with peritoneal carcinomatosis. These guidelines are based on a literature review and expert opinion. The recommended strategy involves a clinical and radiological evaluation, of which CT of the abdomen is a crucial component. The results, together with an analysis of the prognostic criteria, are used to determine whether surgery or stenting is the best option. In most patients, however, neither option is feasible, and the main emphasis, therefore, is on the role and administration of various symptomatic medications such as glucocorticoids, antiemetic agents, analgesics, and antisecretory agents (anticholinergic drugs, somatostatin analogues, and proton-pump inhibitors). Nasogastric tube feeding is no longer used routinely and should instead be discussed on a case-by-case basis. Recent studies have confirmed the efficacy of somatostatin analogues in relieving obstruction-related symptoms such as nausea, vomiting, and pain. However, the absence of a marketing license and the high cost of these drugs limit their use as the first-line treatment, except in highly selected patients (early recurrence). When these

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medications fail to alleviate the symptoms of obstruction, venting gastrostomy should be considered promptly. Rehydration is needed for virtually every patient. Parenteral nutrition and pain management should be adjusted according to the patient needs and guidelines. J Pain Symptom Manage 2014;48:75–91.

Key Words
Peritoneal carcinomatosis, malignant bowel obstruction, palliative care, supportive care, somatostatin analogues, venting gastrostomy, stents, proton-pump inhibitors, corticosteroids

Introduction

Malignant bowel obstruction is described as the association of clinical and imaging evidence of bowel obstruction and a bowel obstruction beyond the ligament of Treitz with incurable intra-abdominal cancer or extra-abdominal primary cancer with intraperitoneal spread (notably breast cancer or melanoma).[1] In some studies, this complication is said to occur in 10%–28% of all colorectal cancers and in 20%–50% of all ovarian cancers.[2–4] Peritoneal carcinomatosis results from tumor cells in the peritoneal cavity. Tumor cells may come from a primary tumor in the peritoneum but in most cases come from the metastasis of abdominal and pelvic malignancies.

Clinical signs usually include abdominal pain or colitis, abdominal distension, nausea, vomiting, and no gas or stools. These symptoms vary depending on the level of the obstruction (Table 1). In patients with advanced or end-stage digestive or gynecologic cancers, bowel obstruction is usually insidious. It evolves over several weeks, with spontaneous remission between episodes.[5]

Bowel obstruction can be either mechanical or functional. Extrinsic mechanical obstruction is the most frequent. It can result from the compression of the digestive lumen by a primary cancerous mass or metastasis (mesenteric or epiploic), radiation-induced fibrosis, or abdominal or pelvic adhesions. Mechanical obstruction can be endoluminal, resulting from a tumor obstructing the bowel lumen or from infiltration because of gastric linitis. Functional obstruction resulting from an impairment of intestinal motility is frequent in patients with tumor infiltration of the mesentery or nerves involved in intestinal motility, in patients with paraneoplasic neuropathy resulting from a secondary paralytic ileus (intra-abdominal infection, intraperitoneal effusion, and intraperitoneal or retroperitoneal pain), and in patients receiving opioid or anticholinergic drugs.

Because of the pathophysiological mechanisms involved, the diagnosis and treatment of bowel obstruction may be challenging. Depending on the patient's general health and response to previous treatments and the location and mechanism of the obstruction and the disease evolution, the goal can either be obstruction relief if possible (with or without surgery) or if not symptom management alone.

These specificities have led several learned societies to consider new studies and to update clinical practice guidelines,[6,7] with the aim of supporting surgeons, gastroenterologists, oncologists, and all medical teams and care providers. The recommendations are related to bowel obstruction with advanced peritoneal carcinomatosis for which complete cytoreductive surgery and intraperitoneal hyperthermic chemoperfusion are no longer relevant. Pain management, rehydration, and parenteral nutrition are not covered here; readers are invited to look at appropriate expert panel evaluations and guidelines.[8–11]

Methods

These recommendations were established following the methodological guide for clinical practice guidelines (CPG) recommended by the French Health Authority (HAS).[12] Briefly, the purpose of the CPG method is to produce a small number of concise unambiguous recommendations graded according to the identified levels of evidence that address the questions asked. The CPG method involves two groups of active participants and has four phases. Because the aim was to develop a practice guideline, a preliminary project scoping

Table 1
Clinical Signs Depending on the Level of Obstruction

Symptoms	Enteral Bowel Obstruction	Colic Bowel Obstruction
Vomiting	Bilious, aqueous	Small volume
	Abundant	Sometimes absent
	No or not very foul-smelling	Foul-smelling, even fecaloid
Pain	Early sign	Late sign
	Periumbilical	Localized
	Brief colicky pain	Colicky pain with sometimes long periods between episodes
Abdominal distension	Sometimes absent	Present
Anorexia	Always	Sometimes absent

phase was written by the chairman of the French Society for Palliative Care.

A multidisciplinary multiprofessional group of 13 professionals was selected by the chairperson and the project officer. They ensured that there was a balanced representation within the groups in terms of the type of practice, the various current opinions, and geographical diversity. The selected members had good knowledge of professional practice in the field relevant to the topic to be investigated. The working group met three times in person in Paris and during seven conference calls, with numerous other e-mails or phone calls being exchanged.

Four Phases of the Project

During the first phase, the working group performed a systematic review and synthesis of the literature. We conducted a systematic review of MEDLINE, Embase, and the Cochrane Library. Key words included: abdominal pain, analgesia, anticholinergic drugs, antiemetics, bowel obstruction, corticosteroids, gastrostomy for peritoneal carcinomatosis, intestinal obstruction, malignant obstruction, nasogastric tube (NGT), octreotide, palliative care, pain, peritoneal carcinomatosis, pump proton inhibitors, scopolamine butylbromide, self-expanding metal stentings, small bowel obstruction, somatostatin analogues, stents, and terminal care. A critical analysis of the retrieved data was made, which allowed the studies to be assigned a level of evidence (Table 2).

In the second phase, the working group drafted the initial version of the guideline.

Table 2
Grading the Guidelines According to the French Health Authority

Level of Evidence Provided by the Literature	Recommendation Grade
Level 1 - Powerful randomized comparative trials - Meta-analysis of randomized comparative trials - Decision analysis based on well-conducted studies	A Established scientific evidence
Level 2 - Less powerful randomized comparative trials - Well-conducted nonrandomized comparative studies - Cohort studies	B Scientific presumption
Level 3 - Case-control studies	C Low level of evidence
Level 4 - Comparative studies with considerable bias - Retrospective studies - Case series	

The evidence report and suggested that graded recommendations were discussed in the light of the data and existing practice (Table 2). An expert consensus of opinion needed the approval of at least 80% of the working group members.

During the third phase, the text was submitted to the five scientific committees of the learned societies for peer review (La Société Française d'Accompagnement et de Soins Palliatifs, La Société Française de Chirurgie Digestive, La Société Française de GastroEntérologie, La Fédération Francophone de Cancérologie Digestive, and L'Association Francophone pour les Soins Oncologiques de Support). An analytical report was written and returned giving a formal opinion of the content and form of the initial draft, in particular its applicability, acceptability, and readability. During Phase IV, the guidelines were amended accordingly by the working group.

Results

Clinical Assessment and Imaging for Diagnosis

CT scan is the gold standard for diagnosis as it has a specificity and sensitivity of more than 90%.[13] CT scans must be performed with submillimeter multidetector devices. Multiplanar reconstructions are absolutely necessary. Spiral

CT scan of the abdomen and pelvis without injection are performed to identify pneumoperitoneum, hematoma, or gastrointestinal bleeding. Then, physicians perform a spiral CT scan with an IV contrast injection with portal acquisition time. High opacification with oral ingestion of contrast agents is useless, even in patients receiving gastric suction because fluid stasis persists beyond the ligament of Treitz. However, the obstructed fluid-filled loops of small bowel in conjunction with IV contrast actually allow for a precise analysis of the gastrointestinal wall and enhancements that might be hidden by an intraluminal contrast agent. Rectum-induced colonic opacification with water-soluble agents is not systematic. It is performed only to ensure that there are no obstacles in the colon.

CT scanning has four main objectives:

1. Diagnose carcinomatosis: Peritoneal carcinomatosis usually results in a mass, nodules or micronodules, peritoneal thickening sheathing the small intestines, or ascites.[14] Lesions are sometimes calcified (ovarian cancer) and best detected on cross-sectional imaging without contrast agent injection. At first, cancerous lesions are usually nonparietal and can then spread to the gastrointestinal tract.
2. Confirm the mechanical obstruction: Mechanical obstruction signs include the identification of a transition zone between flat and distended bowel. The size ratio between the distended and collapsed small bowel distal to the obstacle associated with a flat distal colon without gas and with little fluid is an excellent sign of complete, high bowel obstruction.[15–17] In the study conducted by Deshmulch et al.[18] on small bowel obstruction, the association of a complete, high obstruction (no gas in the small intestine, little or no fluid in the colon) with the absence of the small-bowel feces sign (speckled-like colon contents in the small bowel showing subacute or low grade small-bowel obstruction) is highly predictive of the need for a surgical intervention.
3. Identify a surgical emergency: Complications include perforation, volvulus, or strangulation, which need surgery even in palliative care. Physicians should look for a pneumoperitoneum, signs indicating a volvulus of the small bowel with a "whirl sign"[19] and signs evocative of vascular strangulation such as thickening of the small bowel wall (>3 mm) and/or no enhancement of bowel walls.[20] Fluid effusion is not very significant in cases with carcinomatosis. Parietal pneumatosis and hepatic portal venous gas are late signs.
4. Search for a nonmalignant cause of the obstruction: Non-neoplastic obstructions occur in 15% of patients with an identified carcinomatosis[21] and in 30% according to Woolfson et al.[22] The three main causes can be identified on CT scan. They include adhesions, hernias, and eventration resulting from a previous surgery. Such a diagnosis is difficult and should be based on a precise analysis of the position of the small bowel, colon, and mesenteric vessels.[23] Another cause is radiation enteritis. In these patients, thickening of the small bowel wall is regular, usually segmental and limited to the radiated areas. It is usually associated with an aspect of dense mesenteric fat without any mass or obvious peritoneal nodule.

There are no satisfactory criteria to select patients appropriate for surgery.[24]

Surgical Management. Apart from the above indications, surgery is first considered depending on the underlying cancer, the evolution, and the chemosensitivity. In patients with ovarian cancer, carcinomatosis is found initially in 50% of cases, and the immediate prognosis is far better than in gastrointestinal carcinomatosis and supports surgical interventions.[25] Some decision-making factors should be taken into account to avoid useless and deleterious laparotomies[26–32] (Table 3).

Surgery generally is indicated for patients with an obvious obstacle seen on CT scan, inaccessible for endoscopic prosthesis, with a localized peritoneal infiltration and no massive infiltration of the root of the mesentery or mesocolon, extended pelvic carcinomatosis, and massive ascites. These criteria meet the

Table 3
Poor Prognostic Factors for Surgical Treatment of Bowel Obstruction

- Advanced age
- Poor performance status (OMS 3 or 4)
- Poor nutritional state
- Extent of the malignant disease: diffuse peritoneal carcinomatosis, ascites, palpable masses, multiple obstacles on the small bowel…
- Obstruction of the small bowel rather than colic obstruction
- Previous abdominal or pelvic radiotherapy

unresectability characteristic of ovarian peritoneal carcinomatosis.[33] When there are several obstacles in the small bowel, extensive resection or bypass may be necessary even if these may induce severe complications.[22,34,35] In both cases, the colon must be free at least on the right side, not to lead to abundant secretions with a colostomy associated to a short bowel. A left iliac colostomy can be performed proximal to a pelvic obstacle and is usually well tolerated. Arvieux et al.[36] showed that patients presenting with a stomy, wherever it is located distal to the obstruction, experience uncomplicated postoperative periods with better mean quality of life. Patients who received venting gastrostomy had the lowest complication rate (5%) and good quality of life.

Summary. CT scan of the abdomen and pelvis with injection (when injection of iodinated contrast agent is not contraindicated) is the most relevant examination in cases of obstruction with peritoneal carcinomatosis (Grade C). After the CT scan, surgical advice is necessary (Grade C). A multidisciplinary consulting meeting should be held, when possible, to discuss rare surgical indications (expert consensus). After a surgical emergency has been ruled out (perforation, volvulus, and intestinal ischemia), physicians should select patients appropriately for surgery depending on the type of cancer and prognosis factors (advanced age comorbidities, poor nutritional state, poor performance status ascites, history of radiotherapy, etc.) (expert consensus).

The Role of Stents

Few studies focus on the role of endoscopic prosthesis in the palliative management of obstruction with peritoneal carcinomatosis[37,38] as it is difficult to differentiate carcinomatosis from locoregional recurrence of cancer, especially in ovarian cancer.[39] In contrast, studies focusing on other indications (primary colorectal tumors and gastroduodenal obstructions with primary pancreatic or gastric tumors) are available.[40–45] Technical success rates in these indications vary from 78.8% to 100% and clinical success rates (resolution of obstruction) vary from 83% to 100%. Success rates concerning the resolution of obstruction do not seem significantly different between obstructions by primary tumor or by carcinomatosis.[39,42]

Technical failure is more frequent in long and narrow stenoses (in a recent retrospective study, technical failure was more frequent in a multivariate analysis when the stenosis was more than 4 cm[46]). Complications are rare: migration (8.5%–12.4%), obstruction (0.5%–10%), and perforation (0.5%–4%). Stent migration is even more unusual when the prosthesis diameter (>20 mm) and length are sufficient, and the prosthesis itself is non-coated. Obstructions usually result from either fecal impaction or the spread of tumor and may require the placement of a new endoscopic prosthesis. Perforation is the most severe complication, but it is unusual when there is no previous mechanical dilation (in which case, the prosthesis placement is contraindicated). Use of anti-angiogenic drugs (e.g., bevacizumab) may increase the risk of developing digestive perforation 20-fold.[41] Concurrent radiotherapy also seems to increase the risk.[47] History of radiotherapy (esophagus) increases the complication rate.[48]

In a recent review of the literature,[38] carcinomatosis is not a contraindication to stent placement in patients with a single-point obstruction (single stenosis visible on CT scan) and in whom the lesion is accessible (duodenum-jejunal colon proximal distal, >10 cm from the anal margin).

Summary. When feasible, endoscopic procedures should be preferred to surgery as they have lower morbi-mortality rates (Grade C). The lesion must be accessible with the endoscopic device. Nevertheless, the feasibility of such a procedure is linked to the presence (or absence) of experts and available technology facilities in the hospital. A stent indication should be discussed in collaborative meetings

or in Multidisciplinary Joint-Action Committees if possible (expert consensus).

The Role of NGTs and Venting Gastrostomy?

Nasogastric Tubes. This procedure is considered for patients who suffer from intractable vomiting and/or gastric distention as there is a risk of inhalation. Moreover, a distended stomach can no longer empty itself. Placing an NGT allows time to determine if medical treatments will work (usually 48 hours). However, NGTs are not well tolerated when placed for more than two or three days and can be very uncomfortable when associated with nostril ulceration, esophageal erosion, pharyngitis, and sinusitis. Moreover, NGTs are visible and can be embarrassing for patients. They often prevent patients from being discharged as aspiration devices are not easily set up in patients' homes. Venting gastrostomy must be considered for patients no longer responding to medical treatments or in whom the NGT cannot be removed. The procedure must be considered promptly if it is not contraindicated.[49] The removal of the NGT must not be considered if more than 1 L is secreted (expert consensus).

There is a wide individual difference in tolerance of NGTs: some patients are able to let themselves vomit once a day to avoid the NGT and others prefer to keep the tube placed as it enables them to drink.

Summary. NGTs relieve intractable vomiting and gastric distension. They are absolutely necessary in patients with enteral obstruction. NGTs should not be removed if secretions exceed 1 L/24 h as abundant vomiting will result. Physicians should aim to remove the NGT as soon as possible to minimize patient discomfort (expert consensus).

Venting Gastrostomy. Indications and contraindications of gastrostomy are reported in the recommendations edited by the French Society for Digestive Endoscopy in 2007.[50]

Venting gastrostomy is a rare indication and should be considered as a last resort. Nearly 15% of all gastrostomy procedures are venting gastrostomies.[51] Only one study published between 1995 and 2011 reviewed the efficacy and morbidity associated with venting gastrostomy.[48] Most of the time, reports are of retrospective studies focusing on all indications.[52,53]

Venting gastrostomy is indicated in the presence of a high obstruction resistant to medical treatment, accompanied by intractable vomiting. Studies conducted by the Grenoble University Hospital Center[27,36] showed that venting gastrostomy is usually performed too late. Eighty patients with obstruction and carcinomatosis were treated with steroids and antisecretory drugs. Of them, only 10 patients underwent a gastrostomy when medical treatments were no longer effective. Mean delay for venting gastrostomy was 17 days (range 12–35 days), with a mean survival after the procedure of 13 days (range 6–125 days). These results highlight both the poor prognosis of patients with obstruction and carcinomatosis and the difficulties in deciding whether gastrostomy is indicated and when to perform it without delay. Only the study by Scheidbach et al.[54] showed a longer survival (21 weeks). Even if the different decision-making steps are not well explained, performing early gastrostomy seems to induce better outcomes. This result needs to be confirmed.

Patients must agree to either placement of an NGT or a gastrostomy. Careful explanations must be given about the technique and its potential complications. The venting gastrostomy enables some patients to eat small amounts of food for pleasure, although food must be adapted to allow elimination by the tube. The venting role of the gastrostomy must be emphasized because it may be confused with an alimentary role by patients and practitioners.

Because of the high morbi-mortality of surgery, endoscopic or radiological interventions must be considered (radiological interventions do not require patients to be under general anesthesia). Both methods depend on the available technical facilities and experience of each center.

Most venting gastrostomies are performed endoscopically. In patients with neoplastic ascites, it is mandatory to drain the effusion before performing the gastrostomy.[55] Often enough, patients have parietal masses with advanced stage carcinomatosis, and a history of gastrectomy or abdominal surgery with adherences, which prevent physicians from obtaining clear

gastric transillumination. In these cases, the gastrostomy can be performed surgically, and some surgeons perform gastrostomy almost systematically in the cases of patients with carcinomatosis identified during exploration of an obstruction. Reported complications of gastrostomy include leakage around the tube, gastric bleeding, skin infection, tube blockage, and sometimes peritonitis.[56] Percutaneous transesophageal gastrostomy or jejunostomy recently has been developed as an interesting alternative to nasogastric decompression in patients who are not suitable for gastrostomy, with no complication shown in a small series.[57]

Summary. Venting gastrostomy can be considered as a long-term alternative to maintain an NGT. It must be considered and indicated promptly providing it is feasible and the patient has agreed to undergo the procedure. Percutaneous endoscopic gastrostomy should be preferred although there are some contraindications, principally ascites. Surgical indications remain rare (experts consensus).

Steroid Management

Steroids induce a physiopathological reaction as they have anti-edematous effects. By decreasing the edema around the tumor, steroids decrease intrinsic or extrinsic pressure that contributes to stenosis. They also have a central antiemetic effect and indirect analgesic effects by reducing bowel distension and inflammation.

No study (no new study has been published in the last 10 years) suggests a precise use of steroids. The number needed to treat is six, which means the obstruction was resolved in one of six patients.[58] Morbidity rates in patients treated with steroids are very low. It is difficult to carry out and compare studies as cases differ from one another: presence or absence of peritoneal carcinomatosis, level of obstruction, chemotherapy in the last 28 days, small study samples, and the launching of new drugs for symptom management. Treatments aimed at stopping the cascade—secretion, distension, and bowel hypertonia—are preferred.[28,59]

Methylprednisolone and dexamethasone are prescribed at the moment of the diagnosis: 1−4 mg/kg/d (0.25−1 mg/kg/d of dexamethasone), once-daily IV, or subcutaneous (SC) administration in short courses (<10 days) (expert consensus of opinion). Continuation or discontinuation of treatment depends on the evolution of obstruction (resolution or not) and management of symptoms. Steroids seem even more effective when used as a first-line treatment than when they are started after an obstruction has occurred.[60] The use of steroids in short and repeated courses seems to relieve symptoms. However, the long-term use of steroids is not recommended (expert consensus of opinion).

Summary. Even if evidence is lacking, steroid use may be suggested at the time of diagnosis. They should be administered in short courses of 5−10 days to help manage symptoms and resolve the obstruction. The mean dose is 1−4 mg/kg/d for methylprednisolone or equivalent (expert consensus of opinion).

Antisecretory Drug Management

Anticholinergic Antisecretory Drugs. Scopolamine and butylscopolamine (also known as hyoscine butylbromide [Scoburen®]) have antispasmodic, antiemetic (vestibular center), and antisecretory effects and reduce the volume of gastrointestinal secretions.[61−63] Butylscopolamine is well tolerated as it hardly crosses the blood-brain barrier. This drug has a marketing license for the symptomatic treatment of bowel obstruction in palliative care, with doses ranging from 40 to 80 mg/d administered IV or SC; the dose can be increased to 120 mg/d. Contraindications are those of atropinic drugs: glaucoma and urinary retention with urethra and prostate disorders. The most frequent undesirable effect is dry mouth. Undesirable effects also can include tachycardia and palpitations and sometimes states of agitation or mydriasis with accommodation disorders (frequent with scopolamine). Some physicians use an almost similar medication, glycopyrrolate (Robinul®), which is not available in France.

Summary. Butylscopolamine helps to manage vomiting and colicky pain (Grade C). As it is not very expensive, it is frequently used as a first-line treatment. The mean dose is 60−120 mg/24 h (expert consensus). Scopolamine induces central adverse effects, and it

is not recommended for this indication (expert consensus).

Gastric Antisecretory Drugs. The use of gastric antisecretory drugs, proton-pump inhibitors (PPIs), and histamine antagonists has not been evaluated in bowel obstruction with peritoneal carcinomatosis. This proposal is based on parallels drawn with studies focusing on other indications.

Antisecretory drugs inhibit the secretion of hydrochloric acid by blocking the H + K + ATPase enzyme ensuring H+ ion secretion from the apical pole of the cell (PPIs) or by blocking the membrane receptor H2 against histamine from the vascular pole (anti-H2). Anti-H2s have a rapid, brief, and moderate antisecretory effect. The effect decreases when the patient receives continuous treatments because of a pharmacodynamic phenomenon. PPIs have a strong, dose-dependent antisecretory effect, with a plateau reached between the third and fifth days, which remains stable on prolonged treatment. A meta-analysis[64] focused on the decrease of gastric secretions before surgery under the influence of anti-H2s and PPIs in patients with peritoneal carcinomatosis (normal daily gastric secretion: 1−1.5 L/24 h). Ranitidine proved to be the most effective as it induces a rapid effect. However, we cannot draw conclusions on long-term use. PPIs proved to be more effective in gastroesophageal reflux, esophagitis, and ulcer.[65]

PPIs must be administered once a day before the first meal of the day to induce the best antisecretory effect. In clinical practice, they are administered orally, but the oral route is excluded in patients with obstruction. In healthy patients, the half-life of PPIs in blood is 60 minutes. The IV injection of a bolus does not ensure an increase in intragastric pH as PPI are continuously replaced. IV injection of PPIs should be continuous to inhibit the replaced PPIs and gastric acidity during long periods.[66] Omeprazole can be administered SC.[67,68]

Bile or pancreatobiliary reflux with gastric stasis frequently observed in patients with bowel obstruction increases the risk of developing esophagitis. PPIs are reported to decrease gastric volume and bile reflux and relieve esophagus pain. Omeprazole (20 mg twice daily) is used to manage the parameters of acid reflux and to significantly decrease duodeno-gastro-esophageal reflux.[69] These results argue in favor of the administration of PPIs to patients with carcinomatosis.

As the occurrence of peptic ulcers does not increase when patients receive steroids,[70−72] the concurrent administration of gastroprotective drugs and corticoids may not be systematic. However, some risk factors (history of ulcer, concurrent prescription of nonsteroidal anti-inflammatory drugs or of an antiplatelet dose of aspirin, and severe undernutrition) may lead physicians to prescribe concurrent PPIs.[73,74]

Summary. Gastric antisecretory drugs, like PPIs, seem relevant in patients with obstruction or partial obstruction to reduce gastric secretion or bile reflux and relieve upper digestive symptoms (expert consensus of opinion). They should be administered continuously over 24 hours, which is not always feasible in clinical practice. The IV injection of a bolus is the most frequently used (expert consensus). Omeprazole can be administered SC.

Somatostatin Analogues. Somatostatin is a hormone inhibiting the secretion of GH, TSH, prolactin, and ACTH in the hypothalamus. At the periphery, it also inhibits the secretion of insulin, glucagon, gastrin, and other enteropancreatic peptides such as VIP or substance P. It decreases splanchnic and portal blood flow and small intestine secretions and gastrointestinal motility and increases the gastrointestinal reabsorption of water and electrolytes. Synthetic analogues of natural somatostatin such as octreotide and lanreotide have a long-lasting effect.

Since 1993, several studies have focused on the role of somatostatin analogues in peritoneal carcinomatosis. Most studies are Phase II trials with small samples, between 13[75] and 46 patients[76] (studies on <10 patients were not reviewed). Octreotide is the most studied molecule.[75−81] Only one study focused on lanreotide.[82] Two recent French studies are randomized placebo-controlled trials.[77,82] A recent review of the literature[83] highlighted the interest of octreotide in this indication.

Two interesting studies compared octreotide with other drugs.[62,84]

Somatostatin analogues are effective in treating nausea and vomiting.[28,75–81] However, some of the studies are old and focused on small samples.[75,78,79] All studies showed that omatostatin analogues induce an interruption or a significant reduction of nausea and vomiting. Both French randomized placebo-controlled trials[77,82] proved to be very difficult to carry out. One of them[77] was interrupted because of the lack of patients because palliative care specificities complicated patient inclusion. In the other study,[82] the protocol was not always followed, making the intention-to-treat analysis of the principal criteria difficult to interpret. The results of these two studies should be taken into account with caution although they still favor the efficacy of somatostatin analogues in reducing vomiting. The efficacy of somatostatin analogues also showed the feasibility to remove NGTs[75,77–80,82] (same studies and same comments as above) and an effect on abdominal pain[76] and quality of life.[76,82] Abdominal pain and quality of life were not assessed in all studies. No significant effects on the resolution of obstruction and/or return to normal bowel movements were reported.

Some randomized trials[63,64,84] showed that octreotide was superior to scopolamine derivatives (hyoscine butylbromide) in reducing digestive secretions,[63] nausea,[62,84] vomiting,[62,84] and removal of NGTs.[63] An association of both drugs may be considered. Scopolamine (hyoscine butylbromide) induces a significant effect on colicky pain and also may induce an antisecretory effect. In clinical practice, both treatments can be associated (expert consensus).

The available somatostatin analogues are octreotide[85] and lanreotide.[86] Although they do not have a marketing license, octreotide is recommended in this indication in the Recommendations for Palliative Care by the AFSSAPS.[87]

There are two forms of octreotide (Sandostatin®): an immediate-release (IR) form administered SC (continuous or discontinuous) or by a continuous IV injection[75,76,78,80] and a long-acting release (LAR) form administered intramuscularly (IM), 30 mg every 28 days, with an efficient concentration on the seventh day after the injection. The initial dose of octreotide IR is usually 300 or 600 μg/d,[75,76,78,79] sometimes up to 900 μg[75] Three studies (significant sample groups, from 49 to 68 patients) recommend starting treatment with a 600-μg dose.[76,77,84] If IM octreotide LAR is considered over octreotide IR, the patient should simultaneously receive the IR form during the first six days after the first injection.[77]

There are several forms of lanreotide (Somatuline®), but only one has been studied in patients with bowel obstruction with peritoneal carcinomatosis: the prolonged-release (PR) form, administered IM, 30 mg every 10 days, with two release phases, an IR (first peak two hours after the injection) and an LAR with a new peak on Day 3 with effective concentration until Day 10 to maximum Day 14.[86] Other forms of lanreotide (SC: 60, 90, and 120 mg) were not studied for this indication. For 30 mg lanreotide PR, only one option has been studied for this indication: one IV injection every 10 days.[82]

Both drugs are well tolerated.[76,84] Some side effects have recently been reported: diarrhea and abdominal pain, change in blood sugar levels, and risk of gallstones if the treatment is prolonged.

The efficacy of the drugs is assessed depending on their effects on vomiting. Some older studies focus on octreotide. They recommend that an assessment should be done on Day 3 (in case of inefficacy, doses can be increased) and on Day 5.[75,78,79] A recent Japanese study[76] showed that octreotide administered over three days at doses of 300 μg/24 h produced good clinical outcomes. Good outcomes also were identified in patients who were treated with a double dose (600 μg) on Day 4 if the first-line treatment did not prove effective on nausea and vomiting. This study also showed symptoms kept improving on Day 8. However, on Day 15, symptoms worsened, and this seemed to be correlated with disease progression. In the study comparing octreotide with a scopolamine derivative, most positive outcomes occurred before Day 3 and no more occurred after Day 6.[62,63]

Only one study focused on lanreotide:[82] an assessment was done on Day 7. Because of the 10-day PR, it cannot be stopped before.

Summary. When treatment does not prove effective in controlling symptoms, we recommend discontinuation of octreotide analogues on Day 3 (or Day 6 depending on whether initial doses were increased or not), and lanreotide PR should be discontinued on Day 10 (expert consensus).

Somatostatin analogues can be considered for the treatment of bowel obstruction with peritoneal carcinomatosis. They are more effective than anticholinergic antisecretory drugs in controlling obstruction-induced vomiting. However, as they are rather expensive, they should be administered only after failure of standard treatments including hyoscine butylbromide (expert consensus). Somatostatin analogues can be used as a first-line treatment in patients presenting with an early recurrence of obstruction and in those who responded to somatostatin analogues during previous episodes. When the obstruction is resolved, these drugs should be discontinued except in cases of recurrent episodes (expert consensus).

Antiemetic Management

Especially when associated with antisecretory drugs, antiemetics ensure a decrease in nausea and vomiting induced by bowel obstruction. They are systematically used when these symptoms are reported. Several therapeutic classes with different mechanisms of action are available (Table 4).

Data in the literature concerning their efficacy and when they should be used are often conflicting and are usually based on low-level evidence (mainly expert consensus). When used as a first-line treatment, no advice is available concerning the superiority of any of these antiemetics or whether they should be associated with other treatments.[88–90] Metoclopramide is usually prescribed as a first-line treatment in patients with incomplete obstruction (but not if there is complete obstruction because of the drug's prokinetics effects, which may worsen colicky pain and even increase the risk of perforation).

In patients with complete obstruction, butyrophenones may be used as a first-line treatment although data about their efficacy in controlling nausea and vomiting in palliative care are lacking.[91] They have a direct effect on the vomiting center (chemoreceptor trigger zone). Haloperidol is administered SC, in a continuous infusion or by injection every eight to 12 hours. The IV injection of haloperidol is no longer allowed as it has induced undesirable side effects on cardiac conduction (rare and dose dependent). Droperidol is frequently used for preventing postoperative nausea and vomiting.[92,93] Two recent Cochrane reviews (one on haloperidol and the other on droperidol) revealed that high-quality studies are lacking, and additional studies in palliative care are necessary.[91,94] Butyrophenones are preferred to phenothiazines (chlorpromazine and levomepromazine), which induce severe sedative and anticholinergic side effects although they are particularly effective for intractable vomiting (chlorpromazine).

5-HT3 receptor antagonists are usually used alone or with other drugs when butyrophenones do not prove effective.[95–97] They are serotonin antagonists that induce effects on the chemoreceptor trigger zone of the medulla and on the gastrointestinal tract. They are well tolerated but are expensive. 5-HT3 receptor antagonists have a marketing license for the prevention and treatment of chemotherapy/radiotherapy-induced acute or delayed nausea and vomiting. The dose and duration of treatment are known only for this indication (Table 4).

Treatment plans depend on clinical experience and physicians' habits. No treatment strategy proved superior to another. If we consider there is a dose-effect relationship,[90] antiemetics with different pharmacologic mechanisms of action binding to various receptors (e.g., antiserotoninergic

Table 4
Advised Antiemetics in Bowel Obstruction

Neuroleptics
Metoclopramide (only incomplete obstruction) SC, IV: 30–60 mg/24 h
Haloperidol SC: 5–15 mg/24 h
Chlorpromazine SC, IV: 12–50 mg/24 h
Droperidol SC, IV: 2.5–5 mg/24 h
5-HT3 receptor antagonists
Ondansetron IV: 4–8 mg/d, suppository 16–32 mg/d
Granisetron IV: 3–9 mg/24 h
Tropisetron IV: 5 mg/24 h
Dolasetron IV: 100–200 mg/24 h
Steroids
Scopolamine or butylhyocine of scopolamine
Somatostatin analogues

SC = subcutaneous.

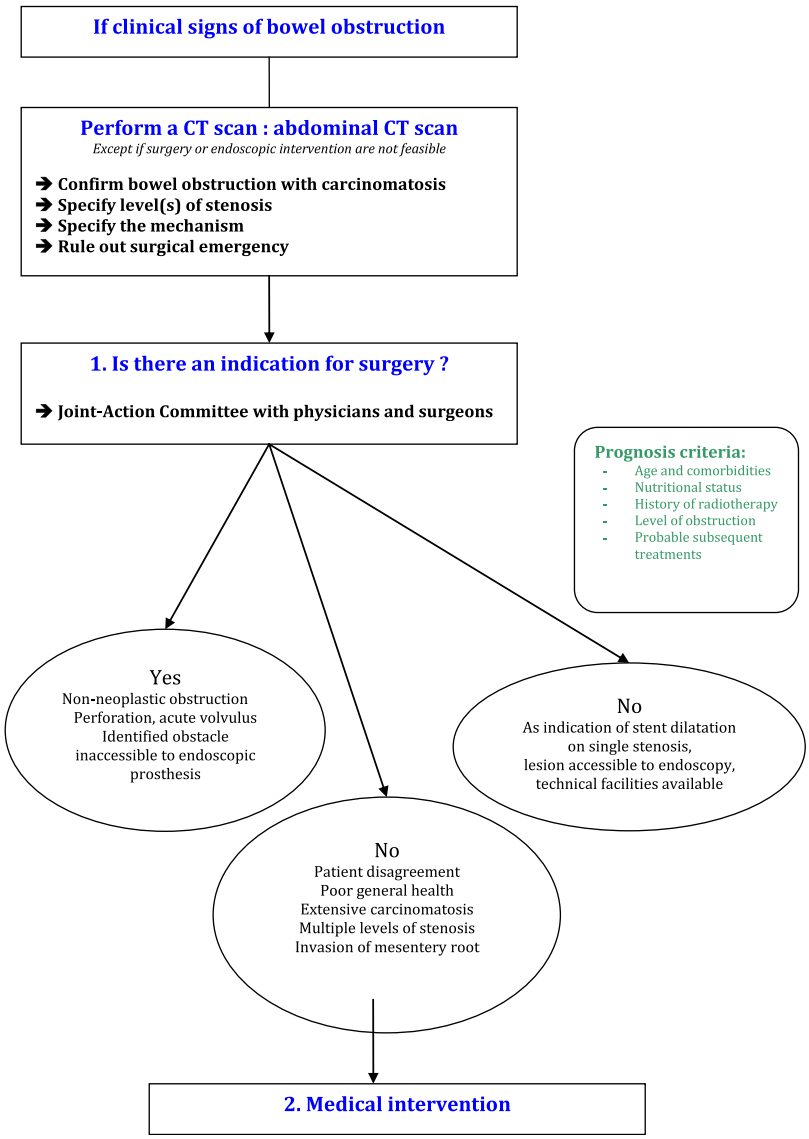

Fig. 1. Decision tree before symptomatic treatments of bowel obstruction.

and dopaminergic inhibitors) can be given together or titrated until clinical response is obtained.

Summary. Haloperidol is usually considered as a first-line treatment. If it does not prove effective, physicians can switch to chlorpromazine although it induces sedative side effects. Droperidol also can be an option (expert consensus). Metoclopramide should be administered only in patients with incomplete obstruction (expert consensus). In patients with intractable vomiting, 5-HT3 receptor antagonists can be considered as a second-line treatment. They can be administered alone or together (expert consensus).

Decision Tree and Protocol for Symptomatic Medical Treatments of Bowel Obstruction With Peritoneal Carcinomatosis

When clinical signs of bowel obstruction are identified, a CT scan should be performed to determine whether surgery is indicated (Fig. 1). If not, a three-stage medical intervention is suggested.

Stage 1. A three-day plan aimed at resolving the obstruction and managing symptoms

Table 5
Bowel Obstruction Protocol, Stage 1

STAGE 1: Day 1 to Day 3
- Fasting patient + IV or SC rehydration
- Symptomatic treatments to be adapted to each case
1. Antiemetics
○ Neuroleptics
○ Metoclopramide contraindicated in complete obstruction
○ Haloperidol SC 5–15 mg/24 h continuous or discontinuous/8–12 h
○ Chlorpromazine IV or SC 12–50 mg/24 h continuous or discontinuous/8–12 h
○ Droperidol IV or SC 2.5–5 mg/24 h continuous or disc/8–12 h second-line treatment: 5HT3 antagonist alone or associated
2. Anticholinergic antisecretory
■ Butylscopolamine 40–120 mg/24 h SC or IV continuous or disc/6–8 h
3. Antisecretory somatostatin analogue: Can be considered as a first-line treatment in cases of early recurrence in patient who responded to somatostatin analogues in previous episodes (see Stage 2)
4. Gastric antisecretory: PPI
■ Continuous IV injection over 24 h or single injection
■ SC is feasible for Omeprazole
5. Steroids: Short courses 5–10 days, IV or SC route
■ 1–4 mg/kg/24 h of methylprednisolone in one single injection
■ or 0.25–1 mg/kg/24 h of dexamethasone in one single injection
6. Analgesics: levels I–II or III, IV, or SC route
7. Nasogastric tube, non systematic
■ Often necessary if abundant vomiting and/or significant gastric distention

SC = subcutaneous; PPI = proton-pump inhibitor

should be initiated (Table 5). Steroids are usually administered in conjunction with other symptomatic treatments (analgesics, antiemetics, and antisecretory drugs). Antisecretory drugs include both gastric antisecretory drugs (PPIs) and anticholinergic agents (butylscopolamine) to induce effects in all parts of the digestive tract. Somatostatin analogue use can be discussed as a first-line treatment in patients with early recurrence and who were responsive to treatment during previous episodes.

Stage 2. To be initiated when Stage 1 fails to resolve the obstruction and persistent nausea/vomiting continue (Table 6). It consists of the administration of a somatostatin analogue if one has not been initiated in Stage 1.

Stage 3. Reassessment after three days of treatment with a somatostatin analogue (Fig. 2). If refractory vomiting persists despite the analogue, the treatment must be discontinued and venting gastrostomy may be suggested and discussed with the patient. If somatostatin analogue administration is successful in controlling vomiting, use of the analogue must be extended.

In all cases, if obstruction has been resolved, all treatments (steroids, anticholinergics, and somatostatin analogues) should be gradually discontinued. A basic laxative treatment may be discussed to limit the risk of recurrence.

IV or SC rehydration is usually initiated immediately. It should be adapted to clinical progression. Parenteral nutrition should be discussed depending on the expected benefit/side effect balance and prognosis factors that have been identified.

This therapeutic management is time limited. It aims at relief without delaying initiation of therapeutic options such as somatostatin analogues and venting gastrostomy to limit repetitive hospitalizations and the use of NGTs, usually placed in the first days after admission but quickly poorly tolerated.

Table 6
Bowel Obstruction Protocol, Stage 2

STAGE 2: Reassessment on Day 4
- If the obstruction is resolved
Reduction until minimal effective dose (even discontinuation) of steroids and anticholinergics
Reassessment of symptomatic treatment
- If obstruction is not resolved and vomiting persist:
Introduction of somatostatin analogue:
Octreotide 600 µg/24 h IV continuous or SC discontinuous/24 h
Or lanreotide PR 30 mg single injection IM/10/24 h
Other medical treatments should be continued depending on clinical efficacy and patient tolerance
- If analogue is used as first-line treatment, see Stage 3

SC = subcutaneous; PR = prolonged release; IM = intramuscularly.

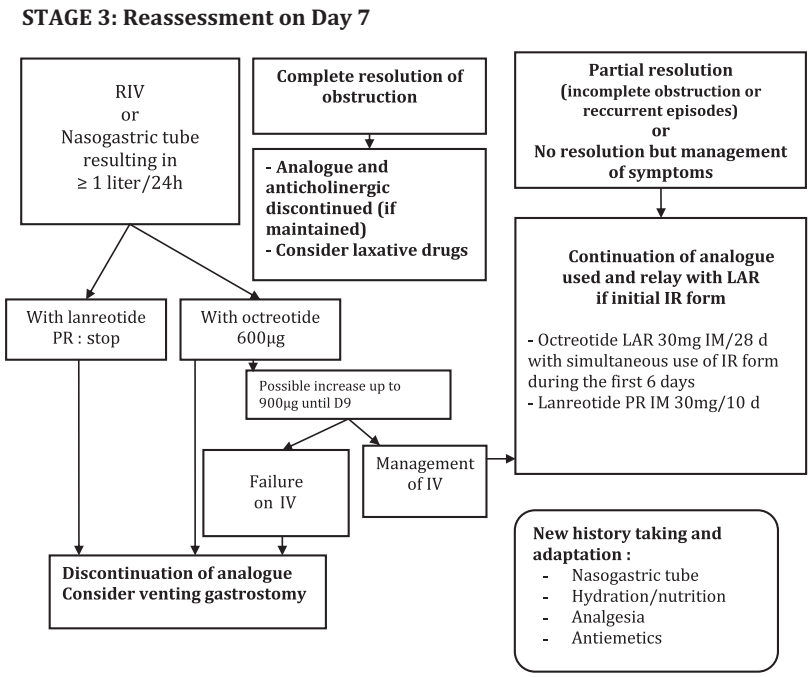

Fig. 2. Bowel Obstruction Protocol, Stage 3. RIV = resistant intractable vomiting; PR = prolonged release; LAR = long-acting release; IR = immediate release; IM = intramuscular; IV = intractable vomiting.

In end-stage patients, who will probably die in the short term, treatments that prove useless and/or disproportionate should be discontinued or never initiated, especially venting gastrostomy and artificial nutrition.

Conclusion

The management of malignant bowel obstruction with peritoneal carcinomatosis has significantly evolved over the past years. It now enables physicians to control symptoms whether the obstruction is resolved or not. Except when surgery or endoprosthesis (when feasible) are particularly indicated, symptomatic medical treatments, especially antisecretory drugs that reduce digestive secretions, are particularly important to relieve patient distress. If intractable vomiting continues, venting gastrostomy is better than a long-term NGT. Encouraging recent studies show symptom control when treated with somatostatin analogues. Analogues should be initiated promptly or even immediately in patients with copious vomiting or early recurrence of obstruction. Because they do not have marketing licenses for this indication and are expensive, analogues are not frequently used as a first-line treatment because patients often respond to less expensive anticholinergic antisecretory drugs. Further research is needed in this area.

Bowel obstruction with peritoneal carcinomatosis is a severe condition as it may be life threatening, but in most cases, comfort can be achieved. Multidisciplinary medical and surgical teams should work together to face obstacles and support the patient and family.

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