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SPECIAL ARTICLE

Medical management of malignant bowel obstruction in patients with advanced cancer: 2021 MASCC guideline update

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Abstract

Background Malignant bowel obstruction (MBO) is a frequent complication in patients with advanced cancer, particularly colon or gynecological malignancies. MASCC previously published a guideline for symptom management of MBO in 2017. This is a 5-year update.

Method A systematic search and review of relevant literature includes a review published in 2010 and 2017. The guideline update used the same literature search process as followed in 2015. The dates of the new search included 2015 up to February 2, 2021. The guidelines involved the pharmacologic management of nausea and vomiting in malignant bowel obstruction (MBO) only. Only randomized trials were included in the updated guideline as evidence. The evidence was reviewed by the panel and the MASCC criteria for establishing a guideline were followed using MASCC level of grading and category of evidence.

Results There was one systematic review and 3 randomized trials accepted as evidence from 257 abstracts. **Octreotide** is effective in reducing gastrointestinal secretions and colic and thereby reduces nausea and vomiting caused by MBO. **Scopolamine butylbromide** is inferior to **octreotide** in the doses used in the comparison study. **Olanzapine** or **metoclopramide** may be effective in reducing nausea and vomiting secondary to partial bowel obstructions. The panel suggests using either drug. Additional studies are needed to clarify benefits. **Haloperidol** has been used by convention as an antiemetic but has not been subjected to a randomized comparison. **Ranitidine** plus **dexamethasone** may be effective in reducing nausea and vomiting from MBO but cannot be recommended until there is a comparison with **octreotide**.

Discussion Octreotide remains the drug of choice in managing MBO. Ranitidine was used in one randomized trial in all participants and so its effectiveness as a single drug is not known until there is a randomized comparison with octreotide. Antiemetics such as metoclopramide and olanzapine may be effective, but we have very few randomized trials of antiemetics in MBO.

Conclusion The panel recommends octreotide in non-operable MBO. Randomized trials are needed to clarify ranitidine and antiemetic choices.

Keywords Nausea · Vomiting · Bowel obstruction · Antiemetics · Octreotide

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Introduction

Malignant bowel obstruction (MBO) is a frequent complication in patients with advanced cancer, particularly colon or gynecological malignancies. Bowel obstruction is either mechanical or functional obstruction that prevents physiological transit and digestion [1]. The prevalence of MBO ranges from 3 to 15% of patients with gastrointestinal cancers, to 20–50% of patients with ovarian cancer, and 10–29% in those with colon cancer [2, 3].The cluster of symptoms associated with MBO include abdominal pain, colic, nausea, and vomiting [4–6]. Obstructions may be complete or partial. Inoperable MBO requires medical management for multiple symptoms. The French Society for Digestive Surgery, the French Society for Gastroenterology, the French Society for Digestive Cancer, and the French Association for Supportive Care in Oncology published guidelines in 2014 which recommended corticosteroids, scopolamine derivatives, histamine (H2) blockers including ranitidine, omeprazole, and somatostatin analogs and antiemetics. Butyrophenones such as haloperidol were preferred to phenothiazines (chlorpromazine and levomepromazine). The recommendations were largely expert opinion except for a few randomized studies involving somatostatin and its long-acting derivative octreotide [7]. A review of the literature by the Palliative Care Study Group of the Multinational Association of Supportive Care in Cancer (MASCC) and a guideline published by MASCC in 2017 also reviewed the evidence for medical management [8, 9]. MASCC has elected to update their guidelines every 5 years. This is an updated and revised guideline based on new randomized trials published in the last 5 years.

Method

A systematic search and review of relevant literature includes a review published in 2010 and 2017 [8, 9]. The first review was done through the MASCC palliative care study group and the second was a formal guideline initiated by the MASCC leadership. The 2017 literature search process was previously published with the guideline (Electronic Supplementary Material). MASCC asked that the guideline be updated 5 years later which is the subject of this manuscript. Individuals with expertise in the field were included in as reviewers and are listed as authors. The guideline update used the same literature search process as followed in 2015. Terms used in the search were largely centered on antiemetics, advanced cancer/palliative, and nausea and vomiting. We wanted trials centered antiemetic management of nausea and vomiting in association with MBO. The dates of the new search included 2015 up to February 2, 2021. The guidelines involved the pharmacologic management of nausea and vomiting in malignant bowel obstruction (MBO) only. Studies which were centered on the non-pharmacological management and surgical management of MBO were excluded. Studies that focused on chronic nausea and vomiting unrelated to MBO are reported separately. Only randomized trials were included as evidence in the updated guideline. Two reviewers (DH, MPD) reviewed the 257 abstracts independently and the studies that are reviewed are those that were accepted by the 2 reviewers.

The evidence was reviewed by the panel and the MASCC criteria for establishing a guideline were followed using MASCC level grading and category of evidence (Tables 1, 2, and 3). Level I evidence is evidence derived from meta-analysis and level II evidence from one well-designed randomized trial with low risk of bias or multiple randomized trials with risks of bias. Level III and IV evidence is derived from non-randomized trials. Grade A guideline evidence is derived from meta-analysis or consistent findings from multiple randomized and non-randomized studies. Level B evidence is generally consistent findings from level II and non-randomized trials. Level C evidence is inconsistent findings in multiple type II, III, and IV studies. Recommendations are based on level I and II evidence and suggested use in non-randomized trial evidence and is based on the panel consensus.

Malignant bowel obstruction literature review

Systematic review 2010

In the systematic 2010 review, several trials reported the following: (1) **Octreotide** was effective in managing nausea and vomiting associated with malignant bowel obstruction; (2) Corticosteroids reduce nausea and vomiting from malignant bowel obstruction; (3) A combination of an **anticholinergic antisecretory drug**, **haloperidol** and **opioid**, relieves symptoms of a bowel obstruction including nausea and vomiting. The studies were mostly single arm prospective studies or case series with few randomized trials [10–24].

MASCC guidelines 2015

In the 2015 guideline, 2 statements were made regarding bowel obstruction: (1) The drug recommended in a bowel obstruction is **octreotide** dosed around the clock and given along with an antiemetic with the committee recommending **haloperidol:** (2) If **octreotide** plus an antiemetic is ineffective, the use of an **anticholinergic** antisecretory agent (**scopolamine butylbromide**, **glycopyrronium bromide**) and/or **corticosteroids** is recommended as either adjunct or alternative interventions**.** The level of consensus and confidence by MASCC criteria was high. For the second, the MASCC consensus was high and confidence moderate except for **corticosteroids** which was low.

Table 1 MASCC levels of evidence

I	Evidence obtained from meta-analysis of multiple, well-designed, controlled studies; randomized trials with low false-positive and false-negative errors (high power).
II	Evidence obtained from at least one well-designed experimental study; randomized trials with high false-positive and/or false-negative errors (low power).
III	Evidence obtained from well-designed, quasi-experimental studies, such as non-randomized, controlled single-group, pretest-posttest comparison, cohort, time, or matched case-control series.
IV	Evidence obtained from well-designed, non-experimental studies, such as comparative and correlational descriptive and case studies.
V	Evidence obtained from case reports and clinical examples.

Literature review 2015–2021

There was one systematic review and 3 randomized trials one of which was a further reporting of outcomes in a study previously reported. A systematic review was published in 2016 which looked at the benefits to octreotide in the management of malignant bowel obstruction [25]. The Cochrane Controlled Trials Register databases were systematically searched; Cochrane risk of bias tool was used. The search identified 420 unique studies. Seven randomized controlled trials (RCTs) met the inclusion criteria (six octreotide studies and one lanreotide); 220 people were given **octreotide** and 207 placebo or **hyoscine butylbromide**. Three RCTs compared somatostatin with placebo and four with **hyoscine butylbromide**. Two adequately powered multicenter RCTs with a low Cochrane risk of bias reported no significant difference between **octreotide** and **placebo** in their primary end points. Four RCTs with high/unclear Cochrane risk of bias reported **octreotide** more effective than hyoscine butylbromide in reducing vomiting. The first negative trial had all patients receive **ranitidine** [26] and is reported in the next paragraph and the second negative trial involved a single injection of l**anreotide**. The trial was only 7 days which may not have allowed the long-acting octreotide reach therapeutic levels and the dropout rate was 39% of 80 patients [27].

One study was published with an update on the quality of life outcomes recently published [26, 28]. This double-blinded randomized multicenter trial compared **octreotide** (600 mcg over 24 h) versus normal saline in 112 patients with MBO. The duration of the study was 72 h. Patient had inoperable MBO. All patients receive **dexamethasone** and **ranitidine**. The **ranitidine** was given parenteral as a continuous subcutaneous infusion. **Hyoscine butylbromide** was available for breakthrough colic. **Haloperidol** was available for nausea. Parenteral opioids were used for pain. The primary outcome was number of patients reported days free of vomiting at 72 h. Nausea was a secondary outcome and measured by NRS. The trial physicians were blinded to allocation. Missing data was imputed. One hundred twelve patients were randomized and 106 were included in the intent-to-treat analysis. Both the placebo and **octreotide** groups had significant improvement in nausea and episodes of vomiting with no difference between treatment groups. The improvement in both groups according to the authors may have been the quality of care on study, the natural history of malignant bowel obstruction, and the routine use of **ranitidine** and **dexamethasone**. The benefits of **ranitidine** are related to reduced gastric secretions which were originally reported by Dr Currow and colleagues in 2009 [29]. Ranitidine also increases in local and circulating somatostatin [30]. This study did not randomized patients to **ranitidine** or placebo; all patients received **ranitidine,** so it is not possible to know how much **ranitidine** contributed to symptom control.

A randomized trial involving 97 patients with ovarian cancer compared **octreotide** to **hyoscine butylbromide** [31]. Randomization was to **octreotide** 0.3 mg/day (**octreotide** group, n = 48) or **hyoscine butylbromide** 60 mg/day (SB group, n = 49) for 3 days through a continuous subcutaneous infusion. **Octreotide** significantly reduced the amount of GI secretions compared with **hyoscine butylbromide**. Nasogastric secretions were significantly reduced in the **octreotide** group, compared with the **hyoscine** group. **Octreotide** rapidly reduced the number

Table 2 MASCC grading of guidelines

Grade of guideline evidence needed	
A	Evidence of type I or consistent findings from multiple studies of type II, III, or IV
B	Evidence of types II, III, or IV and findings are generally consistent
C	Evidence of types II, III, or IV and findings are inconsistent
D	Little or no systematic empirical evidence

Table 3 MASCC categories of guidelines

Recommendation Reserved for guidelines that are based on level I or level II evidence.
Suggestion Used for guidelines that are based on level III, level IV, and level V evidence: this implies panel consensus on the interpretation of this evidence.
No guideline possible: Used when there is insufficient evidence on which to base a guideline. This implies (1) that there is little or no evidence regarding the practice in question, or (2) that the panel lacks consensus on the interpretation of existing evidence.

of daily episodes of vomiting and intensity of nausea compared with **hyoscine butylbromide**.

A small randomized trial (n=16) was reported in a letter [32]. Patients with incomplete bowel obstruction and an average nausea score of greater than 4 on a NRS were randomized to receive either **olanzapine** 5 mg daily or **metoclopramide** 20–30 mg daily for 3 days. The main outcome was the mean nausea score for 3 days using an NRS. The change in nausea score was −3.17 (NRS) for **olanzapine** and −2.38 (NRS) for those given **metoclopramide**. This was not statistically significantly different. The rate of 30% reduction in NRS was not different between treatments. This trial was a small pilot trial and not blinded nor powered for outcomes.

Discussion

There are three questions the panel had in particular regarding the pharmacologic management of nausea and vomiting associated with MBO. How does octreotide work to improve the nausea and vomiting associated with MBO? Is it through reduction in gastric secretions? What dose of hyoscine butylbromide should be used in MBO? How does ranitidine reduce the nausea and vomiting of MBO?

In low doses (50 mcg daily), octreotide prevents motilin in release from M cells within the intestinal mucosa and abolishes antral phase 3 contractions while at the same time improves small-bowel motility by initiating migrating motor complex within the duodenum [33–37]. Octreotide does not appear to influence colonic motility [38]. Higher doses (100 mcg three times daily) increase mouth to cecum transit time and accelerate gastric emptying [39]. Octreotide improves small-bowel motility which improves resolution of postoperative ileus [40–42]. Octreotide at doses of 50–100 mcg daily improves chronic nausea associated with allogenic or autologous bone marrow transplant [43]. Octreotide 50 mcg daily reduces nausea and vomiting associated with systemic scleroderma [44, 45]. Not only does octreotide reduce postoperative ileus but also reduces postoperative pain from abdominal surgery and is opioid sparing [46, 47]. Pain reduction may be through blocking visceral afferent pathways. Somatostatin receptors can be found on lamina I, II, and IV within the dorsal horn which block N-type calcium channels. As a result, bowel distension is better tolerated by individuals on octreotide [33]. The blockade of afferent feedback may be a mechanism by which octreotide reduces nausea. Octreotide has been particularly effective in early postoperative inflammatory small-bowel obstruction. Octreotide not only reduces gastric juices in the intestinal lumen but also reduces intestinal dilatation and ischemia which results from accumulation of intestinal fluid and accelerate the recovery of the intestinal wall circulation and promote resolution of inflammation [48]. There are likely multiple mechanisms by which octreotide reduces nausea and vomiting including reduction in prokinetic intestinal polypeptides such as motilin, resolution of dysmotility, blockade of afferent sensory signals, reduction in bowel inflammation, and improvement of intestinal wall circulation.

Hyoscine butylbromide like glycopyrrolate is a quaternary amine derivative which does not cross the blood-brain barrier and thus does not cause cognitive impairment or delirium. Hyoscine butylbromide is poorly absorbed by mouth and is rapidly cleared parenterally. It reduces cramps at low doses as those used in the MBO studies but requires doses greater than 120 mg daily and closer to 240 mg daily or higher to reduce secretions [24, 49–51]. This may be reason why hyoscine butylbromide was inferior to octreotide. Randomized trials using higher, more therapeutic does will be necessary to clarify this issue.

Ranitidine is a unique H2 receptor (histamine receptor) blocker which is distinctly different in regard to pharmacodynamics than other H2 agents such as famotidine and cimetidine. Ranitidine similar to other H2 receptor blockers reduces gastric acidity and secretions [52]. However, in addition, ranitidine protects the gastric mucosa independent of its influence on gastric acid secretion and inhibits neutrophil activation thus reducing inflammation [53]. Ranitidine increases the release of calcitonin gene-related peptide (CGRP) which within the stomach reduces acid secretion and gastric motility and stimulates blood flow [54–56]. The release of CGRP from the gastric mucosa is unique to ranitidine and does not occur with famotidine or cimetidine [57]. Ranitidine also uniquely increases release of substance P which regulates gastric mucosal blood flow and increases gastric emptying [57]. Ranitidine unlike famotidine or cimetidine has anti-cholinesterase activity which may be the mechanism by which CGRP is increased [58, 59]. What may be an important particularly in the area of MBO management is that ranitidine increases the secretion and expression of somatostatin from and within the gastric mucosa [30]. The increase in CGRP caused by ranitidine increases the release of somatostatin from antral D cells. Famotidine does not increase CGRP nor somatostatin levels [60–66]. Therefore, the administration of ranitidine with subsequent increases in local and circulating somatostatin is likely to be one of the reasons why ranitidine is beneficial in the

management of nausea and vomiting in MBO and why there is no further improvement in symptoms when octreotide is added to ranitidine. However, ranitidine has not been directly compared with placebo.

Summary

1. **Octreotide** is effective in reducing gastrointestinal secretions and colic and thereby reduces nausea and vomiting caused by MBO-multiple RCT with unknown or high risk of bias (level I evidence).
2. The anticholinergic antisecretory drug **scopolamine butylbromide** is inferior to **octreotide** in the doses used in the study (1 RCT) but may be useful for breakthrough nausea and vomiting or colic in patients on **octreotide** (1 RCT) (level III evidence due to the lack of a randomized comparison with octreotide at adequate doses). Doses of hyoscine butylbromide are low for its antisecretory effect. Both glycopyrrolate and hyoscine butylbromide are quaternary amines which do not cross the blood brain and thus cause sedation or confusion and should be considered as an add on drug to those who continue to experience colic. Further studies are needed.
3. Parenteral **ranitidine** plus **dexamethasone** may be effective in reducing nausea and vomiting from MBO but the evidence is too low to recommend its routine use (level III due to the lack of comparison with octreotide). A randomized trial between ranitidine and octreotide is needed.
4. **Olanzapine** or **metoclopramide** are effective in reducing nausea and vomiting secondary to partial bowel obstructions in a small randomized pilot trial (level III evidence). The panel suggests using either drug. Additional studies are needed to clarify benefits. Metoclopramide should be avoided if there is colic or abdominal pain.
5. **Haloperidol** by convention has been used to treat breakthrough nausea and vomiting from MBO in randomized trials but has not be compared with other antiemetics (level III–IV evidence).

MASCC evidence for managing malignant bowel obstruction symptoms including nausea and vomiting

Octreotide is recommended in managing MBO including nausea and vomiting, level 1 evidence with a systematic review. High consensus

Ranitidine may be an effective in managing MBO including nausea and vomiting but further studies are needed, level III evidence based on 1 RCT without a comparison. A comparison of **ranitidine** versus **octreotide** is needed to clarify ranitidine benefits. High consensus

Low-dose **hyoscine butylbromide** is inferior to **octreotide** in managing symptoms of MBO including nausea and vomiting, level II evidence. The panel recommends repeating the comparison with therapeutic doses of **hyoscine butylbromide**. The addition of **hyoscine butylbromide** to **octreotide** may be helpful in those with colic poorly responding to **octreotide**. Further studies using therapeutic doses will be needed to confirm the benefit. High consensus.

Dexamethasone may be effective when added to octreotide or ranitidine and has been part of randomized trials. There is only one meta-analysis with high risk of bias which included observational studies with the primary outcome of clinical resolution of one episode of bowel obstruction within 10 days of diagnosis. Three randomized double-blind placebo-controlled trials were included but nausea and vomiting were secondary outcomes. No data was available from these RCT studies on the improvement or lack of improvement of symptoms [67, 68]. It is reasonable but only can be suggested to add **dexamethasone** in light of the fact that it has been used as standard therapy in recent randomized symptom trials. Future trials are needed to clarify its role in regard to symptom benefits. High consensus

Metoclopramide and **olanzapine** have been compared and can be suggested as antiemetics, but evidence is only in a small randomized trial with a high risk of bias, level II evidence. Well-designed, well powered studies are needed to clarify further both antiemetics' activity. **Haloperidol** has been used as a standard antiemetic in randomized trials and

Table 4 MASCC guideline statement

Guideline statements	LOE	GOE	Guideline
Octreotide should be considered as a front-line treatment for inoperable MBO	I	A	Recommend
Metoclopramide is an active antiemetic in the management of MBO	III	B	Suggestion used
Olanzapine is an active antiemetic in the management of MBO	III	B	Suggestion used
Haloperidol is an active antiemetic in the management of MBO	III–IV	B	Suggestion used
Dexamethasone may be considered in the treatment of MBO	III	B	Suggestion used
Ranitidine may be active in reducing symptoms from MBO	III	B	More evidence is needed

can be suggested but has not been compared with other antiemetics in randomized trials. High consensus

There is no randomized trial evidence that **ondansetron**, **cyclizine, prochlorperazine**, **promethazine**, **chlorpromazine,** or **cannabis** are effective antiemetics in the management of MBO. We recommend against using these agents as first- or second-line antiemetics. High consensus

The MASCC guideline for managing nausea and vomiting in MBO is summarized in Table 4.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00520-021-06438-9.

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