

What is the best available evidence for the safe administration of suppositories in adult patients with neutropenia and thrombocytopenia for constipation management?

This report summarizes evidence that addresses the administration of suppositories, or other rectal procedures (enemas, digital rectal exams) to manage constipation (including opioid induced constipation) in patients with bone marrow suppression. Evidence is presented for all adult patients, with or without cancer, with advanced illness or palliative care.

Key Messages

- Constipation is a common and distressing symptom affecting 30-90% of patients with cancer, advanced illness or receiving palliative care. Constipation has multiple functional and organic causes including the use of opioids for pain relief.
- The management for constipation involves a tailored approach that can include non-pharmacological and pharmacological treatments. Pharmacological interventions include oral laxatives as a first choice of treatment followed by suppositories and enemas. Mu-opioid receptors antagonists are indicated for opioid-induced constipation as a third line option.
- In cancer patients however, bone marrow suppression due to cancer itself and treatments often result in neutropenia and thrombocytopenia. Traditionally, suppositories and enemas are contraindicated in these patients and therefore present a challenge when oral laxatives cannot be administered (in cases of dysphagia) or if they are not effective.
- This review was unable to locate a study evaluating the safety of suppository administration or enemas in adult patients with neutropenia and/or thrombocytopenia for constipation management.
- An expanded search found 11 articles that addressed the use of suppositories, enemas or digital rectal exams in patients with neutropenia and thrombocytopenia. The quality of the articles was generally low to moderate as methods were not usually discussed. Overall, the recommendations from these articles are vague and propagate the longstanding tradition to avoid suppositories, enemas or digital rectal exams with neutropenia and/or thrombocytopenia. Specifically:
 - Most articles indicate a contraindication for enema, suppositories, digital rectal exams and rectal thermometers for treatment of constipation in patients with neutropenia and/or thrombocytopenia. These recommendations were often not referenced or cited expert opinion.
 - One clinical practice guideline stated a contraindication of enemas only (and not suppositories) for second line treatment of constipation in cancer patients [1].
 - One integrative review and one expert opinion cited a lack of evidence to make a recommendation to avoid enemas or digital rectal exams in patients with neutropenia and/or thrombocytopenia [2, 3].
- 10 additional studies did not make any specific recommendations for patients with reduced bone marrow function in the treatment of constipation (including opioid induced constipation) in cancer, advanced/cancer or palliative care populations [4-13].
- Third line treatment for opioid-induced constipation includes mu-opioid receptor antagonists (e.g. Methylnatrexone) which can be administered via a subcutaneous route. However, there is no specific recommendation for patients with neutropenia and thrombocytopenia [14].
- Further studies with higher level designs are required to support practice recommendations for patients with poor bone marrow function in the treatment of constipation with varietal causes.

This summary was requested by:

Lorraine Brown, Nurse in Palliative/Supportive Care Team, and 2nd place winner of the Nursing Dinosaur Contest

This summary includes:

Key findings from a broad collection of recently published literature (from 2005-2019) and other evidence sources.

This summary does not include:

Recommendations, additional information, or detailed description of the interventions in the studies.

1. Background, Methods and Findings

Constipation remains one of the most common and distressing symptoms in patients with cancer, advanced illness, and palliative care, with incidence ranging from 30-90% [3, 4]. It is the third most frequently described symptom in patients at the end of life [15] after pain and anorexia. Constipation is generally defined as the “slow movement of feces through the large intestine resulting in infrequent bowel movements and passage of dry, hard stool” [1] and is a highly subjective experience. Constipation can trigger the development of nausea, vomiting, hemorrhoids, anal fissures, bowel obstruction, urinary retention, confusion and has been linked to delirium [13]. The consequences of constipation add to distress in patients and families and place extra burden on the healthcare system. Constipation can be caused by a number of organic factors, such as specific medications (including opioids), neuromuscular dysfunction, structural issues and pain and/or functional factors such as age, food and fluid intake and lack of privacy [1].

Therefore, constipation management includes a thorough assessment of the presence and potential causes that can guide a tailored approach using non-pharmacological and pharmacological treatments [13]. Generally, stepwise pharmacological interventions are recommended for patients with cancer [5]. This includes oral laxatives as first line, suppositories and enemas as second line and oral or subcutaneous mu-opioid antagonists (if taking regular opioids) as third line of treatment. In cancer patients however, bone marrow suppression due to cancer itself and treatments often result in neutropenia and thrombocytopenia. Some patients experience dysphagia also as a result of cancer or advanced illness/palliative care. Therefore, guidance for nursing practice is needed when first line treatments are not possible and when suppositories/enemas are traditionally contraindicated due to the risk of bleeding or infection in patients with bone marrow suppression.

This rapid review summarizes the best available evidence describing suppository use in patients with neutropenia or thrombocytopenia for the management of constipation (including opioid induced constipation). We opted to broaden the search population to include studies/articles that discussed patients with or without cancer, advanced illness and palliative care. A detailed search strategy was developed by the medical librarian (T. Ekmekjian). Search concepts included Subject Headings and text words (specific search terms are available upon request). Sources included Google, Medline via Ovid (including the Cochrane Database of Systematic Reviews), and CINAHL via EBSCO and limited to results published between 2009 and 2019. The search date was July 17, 2019. A total of 634 titles were reviewed by the librarian. Duplicates and out of scope articles were discarded leaving 28 published articles to be reviewed in more depth. The EIDM-A (S. Castiglione) also searched the grey literature sources including Joanna Briggs Library, UpToDate database, and Google which resulted in 6 additional titles. Citation and reference list searching resulted in an additional 5 titles for a total of 30 full text articles for review. After reading the full text, 6 articles were discarded as being out of scope, not available or in another language other than English or French. 10 articles discussed use of suppositories or enemas in cancer patients but did not make any distinction or mention for patients with bone marrow suppression and therefore were only mentioned in this review. 2 articles discussed mu-opioid receptor antagonists (e.g. Methylnatrexone), a subcutaneous medication for opioid-induced constipation, but with no specific recommendations for patients with neutropenia or thrombocytopenia. Finally, 11 articles were retained and summarized in the review that addressed the use of suppositories, enemas or digital rectal exams in patients with neutropenia and/or thrombocytopenia. Basic quality appraisal was completed for the included articles and each was assigned a level of evidence. The analysis of studies, including appraisal and summary, and the final report were prepared by the EIDM-A and reviewed by the librarian, Chair of the Clinical Practice Review Committee of the MUHC (S. Turcotte) and the nurse in supportive/palliative care team at the MUHC (L. Brown).

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None of the included studies directly addressed the question. No systematic reviews were found. One integrative review was found [3]. The summarized articles were mostly literature summaries, expert opinion, case studies, expert guidelines or evidence-based practice documents that mentioned the use of suppositories, enemas, digital rectal exams or manual evacuation of feces in patients with neutropenia and/or thrombocytopenia [1, 2, 16-23]. The quality was deemed low to moderate with few studies describing their methods. 10 additional articles, which included one systematic review [10], one RCT [13], one pre- post study [9], three case reports or opinion articles [4, 6, 8] and four evidence summaries [5, 7, 11, 12] described management for constipation in cancer or advanced illness/palliative care patients but did not describe specific precautions for patients with neutropenia or thrombocytopenia. A recent Cochrane Systematic Review on Mu-opioid receptors antagonists for opioid-induced bowel dysfunction (constipation) in patients with cancer and/or receiving palliative care did not provide any recommendations for use of these drugs in patients with neutropenia or thrombocytopenia [14]. A table of all the articles found and reviewed is available upon request (sonia.castiglione@muhc.mcgill.ca).

Levels of Evidence (adapted from OHRI KTA Evidence Summary document)

Each piece of evidence presented in this summary is assigned a level:

☀	Platinum	Systematic reviews and meta-analysis
☀	Gold	Randomized controlled trials (RCTs)
★	Silver	Observational studies (non-randomized trials, case-control, time-series, cohort studies, case series) Scoping or integrative literature reviews Qualitative studies
★	Bronze	Expert committee guidelines Non-specified literature reviews Evidence-based summary reports Opinions, commentary or editorials.
⦿	Level of evidence cannot be determined due to lack of methodological information.	

2. Summary of included articles:

Use of enemas, suppositories or other rectal procedures to relieve constipation (including opioid-induced constipation) in patients with neutropenia and/or thrombocytopenia.

⦿ *A recent evidence summary by the Joanna Briggs Institute provided guidance on chemotherapy-induced constipation management. Authors did not address management strategies specific to neutropenic patients. They cautioned the use of manual evaluation of feces in patients with thrombocytopenia. [19]*

★ *In 2007, an integrative review summarized research evidence, guidelines recommendations and expert opinion on evidence-based interventions for the prevention and management of constipation in cancer patients. A comprehensive review of published literature revealed only a few research and expert opinion articles. The authors were unable to make recommendations for practice, but presented a number of strategies effective in the prevention and management of constipation in cancer-patients. None of these interventions addressed cancer patients who were not able to receive oral agents and had bone marrow suppression. According to expert opinion found in this article, the authors cautioned healthcare professionals to avoid rectal agents and manipulation including enemas, suppositories and rectal exams in patients with bone marrow suppression. [3]*

★ *In 2018, the European Society for Medical Oncology (ESMO) published clinical practice guidelines on the diagnosis, assessment, and management of constipation (including opioid induced constipation) in adult cancer patients. The*

guideline promoted a thorough assessment of constipation including causes, impact and physical examination if warranted. Management of constipation was generally based on a balance between strategies for prevention, self-care and prescribed oral and rectal laxative therapies. Generally, self-care included privacy, positioning, increased fluid intake, increased activity and increased mobility within patients' limits and anticipatory management when opioids are prescribed. Oral laxatives were considered first line of treatment. Suppositories and enemas were second line treatment, or first line in cases of a full rectum or faecal impaction. The guideline discouraged enemas in patients with neutropenia or thrombocytopenia. In cases of opioid-induced constipation, when other treatments are unsuccessful, the guidelines suggested new targeted therapies such as Peripherally-Acting Mu-Opioid Receptor Antagonists (PAMORA). The guidelines presented a clinical decision-making algorithm for management of constipation in advanced disease (figure 1). The authors concluded that the quality of evidence in this guideline is considered low as it is based largely on expert opinion, pharmacological reviews and clinical case reports. [1]

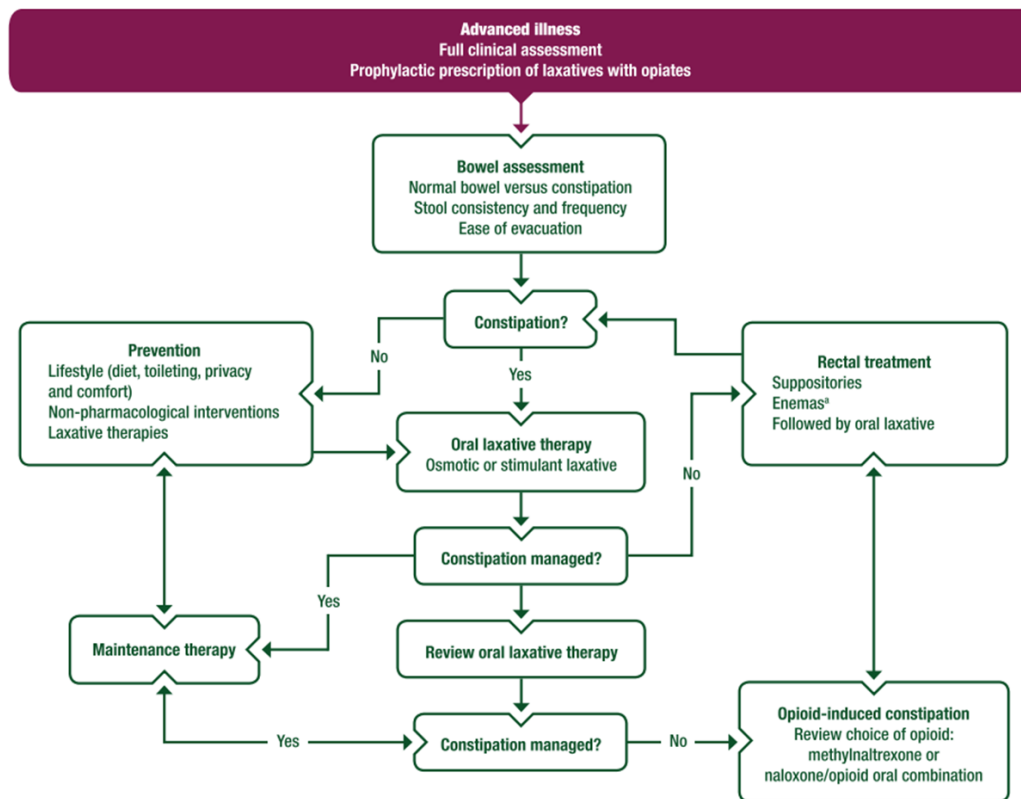


Figure 1. Management of constipation in advanced disease.
^aContraindicated for patients with neutropenia (WBC < 0.5 cells/ μ L).
 WBC, white blood cell count.

★ A case study, reported in 2018, presented a near-fatal medication error with the use of suppositories to treat abdominal pain a cancer patient with neutropenia. The authors admitted to no evidence-based guidelines in the use of suppositories in these patients. They propagated the expert consensus that suppositories should be discouraged due to the risk of infection in immunosuppressed patients. [16]

★ In 2017, a review and opinion article made recommendations for nurses in the management of constipation in adult cancer patients. The author did not report a contraindication for suppository use or enemas for patients with neutropenia or thrombocytopenia. However, the author did advise against rectal exams for assessment and manual disimpaction due to risk of mucosal injury or perforation. There was no description of the process for included evidence in this review. Most recommendations were seemingly based on opinion. [23]

★ Expert opinion was provided for the management of constipation in patients with advanced cancer. Authors promoted oral medications as the first line of treatment. They also cautioned against rectal measures due to the risk of bleeding or abscess formation in patients with neutropenia and thrombocytopenia, however without any supporting evidence. [18]

General use of enemas, suppositories, or rectal examinations in cancer patients with neutropenia and/or thrombocytopenia

★ A very recent (2019) opinion article addressed the common practice of avoiding rectal exams in patients with neutropenia. The authors presented statements by several clinical practice guidelines that provided low level recommendations based on expert opinions. The authors concluded that there is insufficient research to support these recommendations to avoid DRE in patients. [2]

● A Joanna Briggs Institute Practice Summary provided guidelines on recommended practices for enema administration in the community setting. It stated that enema administration is contraindicated in clients with neutropenia or thrombocytopenia. No supporting reference was provided. [17]

★ A literature review conducted in 2013 provided an outline and guidance to infection prevention measures specific to patients, healthcare professionals and visitors in the cancer care setting. They authors did not describe literature search methods. In relation to hygiene, the authors reiterated that experts recommend avoiding digital rectal examinations, rectal thermometers, enemas and suppositories during periods of neutropenia to avoid mucosal breakdown. This review did not specifically address myelosuppressed patients or treatments for opioid-induced constipation. [21]

★ A 2009 guideline for prevention of infection complications recommended against the use of rectal thermometers, enemas, suppositories and rectal exams in hematopoietic cell transplant patients. Expert opinion stated that this contraindication was to avoid skin or mucosal breakdown which may introduce pathogens in immunosuppressed patients. [22]

● In 2007, a conference abstract reported on a review of the prohibition of enemas for the treatment of constipation in patients with thrombocytopenia and neutropenia. The authors noted a lack of research to address the issue in this population. The full presentation was not available, nor was an accompanying published article; attempts to contact the author were unsuccessful. Therefore it is unclear what recommendations for practice were made based on the results of the project. [20]

Constipation management in adult cancer patients or advanced illness/palliative care patients without distinction for neutropenic and/or thrombocytopenic patients.

Level of evidence	Study aim/purpose	Reference
●	Reviewed evidence of prevention and management of side effects in patients receiving opioids for chronic pain	[12]
●	Presented an algorithm for the screening, assessment and management of constipation in adults with cancer	[5]
●	Described evidence-based recommended practices for the management of opioid-induced constipation in palliative care patients.	[11]
●	Described evidence-based recommendations for the care of constipation among patients with advanced cancer	[7]
✱	Reviewed data from randomized-controlled trials of auricular acupressure therapy for preventing constipation in leukemia patients undergoing chemotherapy	[10]
✱	Evaluated whether sweet potato with routine management can alleviate constipation in	[13]

Level of evidence	Study aim/purpose	Reference
★	<i>leukemia patients undergoing chemotherapy versus routine management alone.</i>	
	<i>Described the implementation and outcomes of best practice for constipation assessment and management in advanced cancer patients in a cancer centre.</i>	[9]
★	<i>Examined non-pain physical symptoms that occur in patients undergoing cancer treatments (including constipation) and highlighted clinical approaches to care.</i>	[8]
★	<i>Discussed evidence related to new anti-constipating medications for the general population, for advanced illness and/or opioid inducing constipation</i>	[6]
★	<i>Presented considerations for the management of constipation in palliative care patients.</i>	[4]

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