MASCC RECOMMENDATIONS ON THE MANAGEMENT OF CONSTIPATION IN PATIENTS WITH ADVANCED CANCER

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ABSTRACT

Purpose: The Palliative Care Study Group of the Multinational Association for Supportive Care in Cancer formed a sub-group to develop evidence-based recommendations on the management of constipation in patients with advanced cancer

Methods: These recommendations were developed in accordance with the MASCC Guidelines Policy. A search strategy for Medline was developed, and the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials were explored for relevant reviews / trials respectively. The recommendations were categorised by the level of evidence, and a "category of guideline" based on the level of evidence (i.e. "recommendation", "suggestion", or "no guideline possible")

Results: The Group produced 15 recommendations, with varying levels of evidence, and so varying categories of guideline. The recommendations relate to the assessment, the treatment, and the re-assessment of constipation.

Conclusions: These recommendations provide a framework for the management of constipation in advanced cancer, although every patient needs individualised management.

KEYWORDS

Constipation; neoplasms; palliative care; practice guideline

INTRODUCTION

Constipation is a common problem in patients with advanced cancer, and is the cause of significant morbidity in this group of patients. However, observational studies suggest that constipation is not well managed in patients with advanced cancer [1]. The reasons for the latter are multiple, and include inadequate assessment, inappropriate treatment, and inadequate re-assessment (and assess response to treatment). Moreover, non-adherence to clinical guidelines [2], and non-adoption of new interventions [3], appear to be common occurrences.

On the basis of the above, the Palliative Care Study Group of the Multinational Association for Supportive Care in Cancer (MASCC) formed a sub-group to develop evidence-based recommendations on the management of constipation in patients with advanced cancer. [The group received no internal / external funding to support the process]. This paper gives an overview of constipation in patients with advanced cancer, the methodology involved in developing the recommendations, and the evidence to support the recommendations (and the grading of the evidence).

At the time the Group started the project there were no up-to-date guidelines on the management of constipation in patients with advanced disease. However, in the interim, the European Society of Medical Oncology (ESMO) have published analogous guidelines [4]. Our recommendations complement the ESMO guidelines, but they provide more detailed guidance on the pharmacological management of refractory constipation (of differing aetiology).

BACKGROUND

Definition

The Oxford Concise Medical Dictionary defines constipation as “a condition in which bowel evacuations occur infrequently, or in which the faeces are hard and small, or where passage of faeces causes difficulty or pain” [5]. Indeed, the term “constipation” means different things to different people [6], which has implications for the management of constipation. For example, a Swedish survey of the general population reported that 23.8% female respondents, and 24.3% male respondents, considered “straining in connection with bowel movement” was not indicative of constipation [7]. Similarly, a Korean survey of constipated individuals

reported that 48.3% respondents considered “using fingers to help empty your bowel” was not indicative of constipation [8].

Aetiology

The Rome Foundation categorise constipation as being either functional constipation, or secondary constipation [9]. Functional constipation is a heterogeneous phenomenon, and can be subdivided into normal-transit constipation, slow-transit constipation, and defaecatory or rectal evacuation disorders [9]. The risk factors for functional constipation include a positive family history, low levels of dietary fibre, and low levels of physical activity [9]. Secondary constipation may have a variety of different causes, including gastrointestinal diseases (e.g. diverticulosis, irritable bowel syndrome), neurological / psychiatric diseases (e.g. dementia, depression), other systemic diseases (e.g. diabetes, hypothyroidism), and / or medications (e.g. antacids, diuretics) [6].

Opioid-induced constipation is a subtype of secondary constipation, with a distinct pathophysiology (Box 1), which is primarily a peripheral effect, and primarily a mu-opioid receptor effect [10]. Opioid-induced constipation appears to be more common in patients with cancer pain (than non-malignant pain) [9], may be influenced by genetic factors [11], and may be influenced by the type of opioid utilised [12]. However, opioid-induced constipation does not appear to be particularly influenced by the dose of opioid utilised [13]. Opioid-induced constipation tends to be a chronic side effect, although some patients appear to develop tolerance over time [13]. Unsurprisingly, the pathophysiology has important implications in relation to the management [14].

INSERT BOX 1 ABOUT HERE

Epidemiology

Constipation is a common problem, with most people experiencing the symptom at some point in their life. The reported mean prevalence of functional constipation in the general population is 14% (range 1.9-40.1%), with a mean prevalence of 15% using self-assessment, and a mean prevalence of 6.8% using the Rome Foundation diagnostic criteria (i.e. Rome III diagnostic criteria) [15].

The reported prevalence of constipation in patients with advanced cancer is 32-87%, which reflects variable methods of assessment as well as different study populations (e.g. inpatients generally have a higher prevalence than outpatients) [16]. Similarly, the reported prevalence of opioid-induced constipation in patients with cancer pain is 5-97%, which again reflects variable methods of assessment as well as different study populations [17].

Clinical features

The clinical features vary from patient to patient, and include symptoms relating to constipation, and / or symptoms resulting from the complications of constipation (i.e. local, systemic).

An American survey of constipated (functional constipation) individuals reported the frequency of different symptoms relating to constipation: straining (79%), "gas" (74%), hard stool (71%), abdominal discomfort (62%), infrequent defaecation (57%), bloating (57%), sensation of incomplete evacuation (54%), abdominal pain (48%), rectal pain (41%), and sudden urge for defaecation (35%) [18]. Moreover, 52% of individuals reported that constipation significantly affected their quality of life (i.e. "somewhat", "a lot", or "a great deal") [18].

The local complications of constipation include faecal impaction, faecal leakage / "overflow diarrhoea", gastrointestinal obstruction, gastrointestinal perforation, rectal prolapse, haemorrhoids, anal tears, rectal bleeding, urinary tract infection, and urinary retention [16]. Patients may also experience upper gastrointestinal problems such as halitosis, anorexia, early satiety, nausea and vomiting, and gastro-oesophageal reflux ("heartburn"). The systemic complications of constipation include general malaise, confusion / delirium, and headache [16]. Uncommonly, constipation can indirectly cause the death of an individual (e.g. faecal impaction causing gastrointestinal perforation; straining causing pulmonary embolism) [19,20].

Constipation is associated with various psychological problems, including anxiety, depression, and even "catastrophic thinking" (e.g. "I thought you would die, blow up inside") [21]. Moreover, it can lead to negative social outcomes such as avoidance of family / friends, and avoidance of public places (and so social isolation) [22].

Constipation is also associated with a significant health economic burden: constipation leads to increased “direct costs” (e.g. costs of intervention, costs of healthcare professional), and increased “indirect costs” (e.g. costs of travel, costs of decreased productivity), which impacts on the patient, the health service and the wider society [23].

Of concern patients with opioid-induced constipation may reduce the dose of opioid analgesic, or even stop the opioid analgesic, in order to overcome the associated distress and discomfort (which usually results in worse cancer pain) [24].

METHODS

The aim of the Group was to develop comprehensive, clinically-relevant, evidence-based recommendations on all aspects of the management of constipation in patients with advanced cancer. Thus, it was agreed that the recommendations could include ones supported by “high” levels of evidence (e.g. systematic reviews), as well as ones supported by “low” levels of evidence (e.g. expert opinion), if the topic was deemed to be clinically-relevant.

The recommendations were developed in accordance with the MASCC Guidelines Policy [25]. The Group adopted the National Cancer Institute (NCI) definition of advanced cancer (i.e. “cancer that has spread to other places in the body and usually cannot be cured or controlled with treatment”) [26], and data was included from studies involving cancer patients still receiving anti-cancer treatment, and also cancer patients only receiving palliative care (or both modalities).

A search strategy for Medline was developed (Appendix 1), and the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials (CENTRAL) were explored for relevant reviews / trials respectively [27,28]. The review of the published literature was restricted to papers written in English, and to papers relating to adult (> 18 years) humans.

All abstracts identified by the search of Medline (1946 - present) were downloaded into a reference management software package. These abstracts were independently assessed for relevance by the two main authors (AD, CL), and if one author deemed the abstract relevant, then the full text of the article was obtained. These articles were independently assessed for inclusion by the two main authors. All the authors were involved in assessing the randomised

controlled trials in the CENTRAL, and the two main authors were involved in assessing the systematic reviews in the Cochrane Database of Systematic Reviews.

Whenever possible the recommendations were based on data from patients with advanced cancer. However, when no data was available, or only poor quality data was available, data from other populations was extrapolated (if deemed appropriate). For example, the evidence for the peripherally acting mu-opioid receptor antagonists is mainly from studies involving patients with non-malignant pain (rather than patients with cancer pain). However, it is generally accepted that the efficacy of such drugs is not related to the underlying condition [29], although the tolerability may be influenced by the underlying condition and/or co-morbidities.

The recommendations were characterised by a level of evidence (i.e. I, II, III, IV, or V), and a "category of guideline" based on the level of evidence (i.e. "recommendation", "suggestion", or "no guideline possible") (Appendix 2) [25]. The recommendations were independently characterised by the two main authors (AD, CL), and a consensus reached in the case of any disagreement. [All of the authors agreed with the recommendations / characterisations of recommendations].

RESULTS

The searches were last undertaken on 19th April 2019. The Medline search identified 2775 references, and 260 full text articles were retrieved (and reviewed). The search of the Cochrane Central Register of Controlled Trials (utilising the keywords "constipation" and "cancer") identified 1925 references, and 54 articles were formally reviewed. Similarly, the search of the Cochrane Database of Systematic Reviews (utilising the keyword "constipation") identified 23 references, and 10 reviews were formally reviewed.

The Group produced 15 recommendations (see below), with varying levels of evidence, and so varying categories of guideline.

RECOMMENDATIONS

The recommendations of the Group are summarised in Table 1 (with the levels of evidence, and the categories of guideline). Moreover, the Group recommend that all pharmacological

interventions are used in accordance with their Summary of Product Characteristics, i.e. that prescribers follow the prescribing guidance (e.g. dose, dose frequency), and take note of relevant contraindications, cautions, interactions, and adverse effects.

INSERT TABLE 1 ABOUT HERE

Recommendation 1 - All patients with advanced cancer should be regularly assessed for constipation [Level of evidence - V; category of guideline - suggestion].
The objectives of assessment are to determine: a) the presence of constipation; b) the aetiology of constipation (i.e. functional, secondary); and c) other factors that may influence the choice of intervention. Inadequate assessment may result in initiation of inappropriate interventions (or even contra-indicated interventions).

The assessment of constipation involves primarily taking a detailed history, and performing an appropriate examination (i.e. clinical assessment). The history should include the questions outlined in Box 2 [6,9], and the use of the Bristol Stool Chart (to assess stool consistency) [30]. The examination should include an abdominal examination, and ideally a digital rectal examination [6,31].

INSERT BOX 2 ABOUT HERE

The Rome Foundation diagnostic criteria are generally employed to diagnose functional gastrointestinal disorders. The Rome IV criteria for functional constipation are shown in Table 2 [9]. Of note, the validation studies of these criteria reported a relatively low sensitivity of 32.2%, a relatively high specificity of 93.6%, and "moderate" reliability [32]. The new Rome IV criteria for opioid-induced constipation are also shown in Table 2 [9]. Currently, there are no published validation studies of these criteria.

INSERT TABLE 2 ABOUT HERE

Observational studies suggest that plain abdominal X-rays may be helpful in assessing patients with constipation [33], including patients with advanced cancer [34]. However, more specialised gastrointestinal investigations should be limited to patients with "resistant"

constipation in patients with advanced cancer (and should be undertaken by gastroenterologists with an interest in constipation) [9].

Recommendation 2 - The management of constipation should be individualised [Level of evidence - V; category of guideline - suggestion].

The management of constipation should be individualised, and depends on: a) aetiology of constipation (e.g. functional, opioid-induced); b) clinical features of constipation (e.g. faecal impaction, stool in rectum); and c) patient-related factors (e.g. personal preferences, co-morbidities).

Recommendation 3 - Patients should be offered adequate privacy, and appropriate equipment (e.g. commode, foot stool), to promote defaecation [Level of evidence - V; category of guideline - suggestion].

Observational studies of patients with advanced cancer have shown an association between constipation and lack of privacy (for defaecation) [35]. Hence, whenever possible patients should be supported to defaecate in a private toilet, rather than at the bedside (or within the bed). Indeed, bedside commodes should only be used if the patient has mobility problems, and bed pans should only be used if the patient is on strict bed rest. Defaecation may be facilitated by adopting the "correct" toilet position (i.e. semi-squatting position, knees above hips, leaning slightly forward) [36], and this can be facilitated by the use of a foot stool [9]. It is essential that a foot stool is used whenever a raised toilet seat is employed.

Recommendation 4 – Lifestyle changes (e.g. dietary fibre, exercise) have a limited role in patients with advanced cancer [Level of evidence - V; category of guideline - suggestion].

Observational studies of patients with advanced cancer have also show an association between constipation and inadequate nutrition (low fibre diet), inadequate hydration, and decreased physical activity [35]. Moreover, there is evidence that increasing fibre intake, increasing fluid intake (in dehydrated patients), and increasing physical activity may improve functional constipation (but not opioid-induced constipation) [9]. However, these strategies are generally unsuitable for patients with advanced cancer [16], and indeed there is no evidence that these strategies are effective in this group of patients.

Recommendation 5 - Reversible causes of constipation should be treated, and potential aggravating factors should be minimised [Level of evidence - V; category of guideline - suggestion].

In some cases of secondary constipation it will be possible to treat the underlying condition, or discontinue the constipating medication, and so ameliorate the constipation. It should be noted that reducing the dose of opioid invariably does not improve opioid-induced constipation, although "switching" the opioid sometimes improves opioid-induced constipation [37].

Recommendation 6 - Conventional laxatives should be considered as first-line treatment in patients with functional constipation [Level of evidence - I; category of guideline – recommendation; data primarily from the general population].

Currently, there is relatively little data on the use of conventional laxatives in patients with advanced cancer. Thus, the Cochrane systematic review of laxatives for the management of constipation in people receiving palliative care (almost exclusively patients with advanced cancer) concluded that "there was no evidence on whether individual laxatives were more effective than others or caused fewer adverse effects" [38].

However, on the basis of data in the general population [39,40], expert opinion (gastroenterology) [6,41], expert opinion (palliative care) [42], and extensive clinical experience in patients with advanced cancer, the group recommend the use of polyethylene glycol formulations as the first-line treatment for constipation in patients with advanced cancer. [It should be noted, however, that none of the studies in the aforementioned Cochrane systematic review involved polyethylene glycol formulations [38]].

Nevertheless, as stated above, the management of constipation should be individualised, since certain practical issues can limit the use of polyethylene glycol formulations (e.g. volume of fluid, taste / consistency), as well as certain adverse effects (e.g. diarrhoea, abdominal distension) [2]. The same considerations apply to all other conventional laxatives (and indeed all interventions for constipation). Table 3 shows the British National Formulary categories of laxatives with examples for each category [43].

INSERT TABLE 3 ABOUT HERE

Recommendation 7 - Conventional laxatives should be considered as first-line treatment in patients with secondary constipation [Level of evidence - V; category of guideline - suggestion].

Management of secondary constipation primarily involves treating the underlying condition. If this is not possible, or if the patient remains constipated, then management of secondary constipation should follow that of functional constipation (with the exception of opioid-induced constipation - see below).

Recommendation 8 - If patients with functional constipation / secondary constipation do not respond to first-line conventional laxatives, then re-assess the patient and consider adding or switching to another conventional laxative or specialist medication (e.g. linaclotide, lubiprostone, prucalopride) [Level of evidence - V; category of guideline - suggestion].

If patients do not respond to optimal dosing of first-line conventional laxatives, then the options for ongoing management involve the use of conventional laxatives from a different class of drug (Table 3), or a more "specialist" medication (e.g. linaclotide, lubiprostone, prucalopride) [44]. The latter should generally be prescribed / monitored by clinicians with experience in utilising such specialist medication.

Recommendation 9 - Peripherally-acting mu-opioid receptor antagonists (PAMORAs) should always be considered in patients with opioid-induced constipation [Level of evidence - I; category of guideline - recommendation; data from patients with cancer, and patients with advanced disease].

The peripherally-acting mu-opioid receptor antagonists (PAMORAs) reverse the effects of opioids on the gastrointestinal tract, and so in theory should be the optimum treatment for opioid-induced constipation. A number of different PAMORAs have been developed to treat opioid-induced constipation, including subcutaneous methylnaltrexone [45], oral methyl-naltrexone [46], oral naloxegol [47], and oral naldemedine [48]. Studies of PAMORAs have been undertaken in patients with advanced disease, and also in patients with cancer pain (as opposed to non-malignant pain). Of note, there is no data to suggest that the efficacy / tolerability of PAMORAs is population-dependent.

The Cochrane systematic review of mu-opioid antagonists for opioid-induced bowel dysfunction in people with cancer and people receiving palliative care concluded that "there

is moderate-quality evidence that methylnaltrexone improves bowel function in people receiving palliative care in the short term and over two weeks, and low-quality evidence that it does not increase adverse events", and that "there is moderate-quality evidence to suggest that, taken orally, naldemedine improves bowel function over two weeks in people with cancer and OIBD (*opioid-induced bowel dysfunction*) but increases the risk of adverse events" [49].

Another systematic review of treatments for opioid-induced constipation concluded "mu-opioid receptor antagonists to be safe and effective for the treatment of OIC" [50]. This systematic review included a larger range of studies than the Cochrane systematic review (23 versus eight randomised controlled trials) [49], and calculated numbers needed to treat (NNT) of 3.4 (95% CI: 3-6) for methylnaltrexone, 7 (95% CI: 4-26) for naloxegol, and 5 (95% CI: 4-8) for naldemedine, and the number needed to harm of 20 for all medications [50]. The response to PAMORAs was affected by the dose of opioid (increased efficacy in patients on higher doses), and the previous response to laxatives (increased efficacy in patients "refractory to laxatives") [50]. It should be noted that the aforementioned NNTs were calculated using different primary endpoints (and so are not directly comparable) [50].

In 2015, the National Institute for Health and Care Excellence (NICE) reviewed the clinical and health economic data on oral naloxegol, and concluded that "naloxegol is recommended, within its marketing authorisation, as an option for treating opioid induced constipation in adults whose constipation has not adequately responded to laxatives" [29]. The technology appraisal guidance states that "an inadequate response is defined as opioid-induced constipation symptoms of at least moderate severity in at least 1 of the 4 stool symptom domains (that is, incomplete bowel movement, hard stools, straining or false alarms) while taking at least 1 laxative class for at least 4 days during the previous 2 weeks".

Conventional opioid antagonists (e.g. naloxone) have been used to manage OIC [51], and have even been incorporated into analgesic formulations to prevent / manage OIC [52]. However, conventional opioid antagonists particularly in high doses may reverse analgesia, and precipitate withdrawal (and so their role is somewhat limited) [51].

Recommendation 10 - If patients with opioid-induced constipation do not respond to PAMORAs, then re-assess the patient and consider adding or switching to a conventional

laxative or specialist medication (e.g. lubiprostone, prucalopride) [Level of evidence - V; category of guideline - suggestion].

Systematic review data suggests that many patients with opioid-induced constipation do not achieve an adequate response with PAMORAs [49,50], which may reflect the fact that the constipation is not opioid-induced, or more likely that the constipation is multi-factorial in aetiology [53]. Thus, some patients will benefit from the addition of a conventional laxative to the PAMORA, whilst others will require the substitution of a conventional laxative for the PAMORA. Of note, lubiprostone and prucalopride have efficacy in opioid-induced constipation (as well as functional constipation) [54,55].

Recommendation 11 - Patients prescribed opioid analgesics should be routinely co-prescribed laxatives (or a PAMORA) [Level of evidence - IV; category of guideline - suggestion].

As constipation is a common adverse effect of opioid analgesics, it is recommended that patients starting opioid analgesics should be co-prescribed conventional laxatives [56,57]. Surprisingly, there is only limited evidence to support this recommendation [58].

Currently, there is no data to support the co-prescribing of PAMORAs, although in theory this would be a more effective strategy to prevent opioid-induced constipation (than the co-prescribing of conventional laxatives) [14].

Recommendation 12 - Suppositories / enemas should only be used in patients with evidence of stool in the rectum and / or descending colon that have not responded to other interventions [Level of evidence - V; category of guideline - suggestion].

The evidence base for rectal interventions (i.e. suppositories, enemas) is somewhat limited, and there are no randomised controlled trials in patients with advanced cancer [38]. Rectal interventions are generally reserved for patients that have not responded to other interventions [6,42], with suppositories used in patients with stool in the rectum, and enemas used for patients with stool in the descending colon [4]. A variety of different formulations are available (Table 3) [4,43], and there are a number of local and systemic contraindications (e.g. intestinal obstruction, thrombocytopenia) [4].

Trans-anal irrigation (TRI) may have a role in some patients, but the evidence to support its use in clinical practice is limited [59].

Recommendation 13 - Other interventions should generally only be used in patients with "resistant" constipation [Level of evidence - V; category of guideline - suggestion].

A wide range of other interventions have been used to manage constipation in the general population, and in patients with advanced cancer, i.e. traditional remedies, complementary therapies, and other pharmacological interventions. Interventions that have been reported as being effective in patients with advanced cancer include acupuncture (and associated techniques) [60], aroma massage [61], petroleum jelly [62], amidotrizoate / diatrizoate [63], and neostigmine [64]. However, the evidence base (and indeed experience) with these interventions is more limited than with previously discussed interventions.

Recommendation 14 - All patients with constipation should be regularly re-assessed [Level of evidence - V; category of guideline - suggestion].

The objectives of re-assessment are to determine: a) changes in the clinical condition; b) the effectiveness of any intervention; and c) assess the tolerability of any intervention. Inadequate re-assessment may result in continuation of ineffective interventions (and persistence of constipation).

An expert consensus panel has recommended that the Bowel Function Index be used to assess the effectiveness of interventions for opioid-induced constipation, with a score of > 30 triggering a change in intervention (as this represents an "inadequate response") [65,66]. However, other outcome measures may be more appropriate in some individuals [65].

Recommendation 15 - Patients with ongoing "resistant" constipation should be referred to a specialist for further investigation / management [Level of evidence - V; category of guideline - suggestion].

CONCLUSION

Constipation is a common problem in patients with advanced cancer, and is the cause of significant morbidity in this group of patients. The recommendations in this paper are wherever possible based on studies in patients with advanced cancer, and if such data was not available extrapolated from other groups of patients. However, patients with advanced cancer are different from other groups of patients, including patients with other life-limiting conditions. Thus, further research is required to validate these recommendations.

CONFLICT OF INTEREST

ADavies has received personal fees and research funding from Kyowa Kirin; CL has received personal fees from Kyowa Kirin; ADickman has received personal fees from Kyowa Kirin; DF has received personal fees from Novartis, Pfizer and Roche.

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APPENDIX 1 - Medline search strategy

1. Constipation – mesh

OR (search terms 2-50)

2. Defecation – mesh
3. Laxatives – mesh
4. Cathartics – mesh
5. Aperients – key word
6. Bulk forming laxatives – keyword
7. Ispaghula husk – keyword
8. Methylcellulose – mesh
9. Sterculia – mesh
10. Frangula – mesh
11. Chloride channel agonists – mesh
12. Lubiprostone – mesh
13. Osmotic laxatives – keyword
14. Lactulose – mesh
15. Macrogol – keyword
16. Polyethylene glycols – mesh
17. Magnesium hydroxide – mesh
18. Sodium acid phosphate – keyword
19. Serotonin 5-HT4 receptor agonists – mesh
20. Prucalopride – key word
21. Stimulant laxatives – keyword
22. Bisacodyl – mesh
23. Co-danthramer – keyword
24. Dantron – keyword
25. Poloxamer – mesh
26. Co-danthrusate – keyword
27. Glycerol – mesh
28. Senna – keyword
29. Senna extract – mesh
30. Senna plant – mesh
31. Anthraquinones – mesh

32. Sodium picosulfate – keyword
33. Opioid receptor antagonists – keyword
34. Narcotic antagonists – mesh
35. Peripherally acting mu opioid receptor antagonist – keyword
36. Methylnaltrexone – keyword
37. Naloxegol – keyword
38. Softening drugs – keyword
39. Arachis oil – keyword
40. Docusate sodium – keyword
41. Dioctyl sulfosuccinic acid – mesh
42. Liquid paraffin – keyword
43. Mineral oil – mesh
44. Bowel cleansing – keyword
45. Enema – mesh
46. Suppositories – mesh
47. Dietary fiber – mesh
48. Psyllium – keyword
49. Fecal impaction – mesh
50. Disimpaction – key word

AND (search terms 51-52)

51. Neoplasms - mesh

OR

52. Cancer – key word

APPENDIX 2 – MASCC criteria for grading recommendations

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 nonrandomized, 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

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

Decreased small bowel motility
Decreased electrolyte & water secretion small bowel
Increased tone ileocaecal valve
Decreased large bowel motility
Increased electrolyte & water absorption large bowel
Increased tone anal sphincter
Reduced anorectal sensitivity (to distension)

Box 1 - Pathophysiology opioid-induced constipation.

Frequency of bowel movements?
Straining with bowel moments?
Consistency of stool*?
Sensation of incomplete evacuation?
Sensation of blockage in rectum / anus?
Current / previous use of laxatives?
Current / previous use of other measures (e.g. traditional remedies, complementary remedies)?
[Change in bowel function since starting opioid analgesia?]

* Utilise Bristol Stool Chart

Box 2 – Questions for assessing constipation.

- **All patients with advanced cancer should be regularly assessed for constipation [Level of evidence - V; category of guideline - suggestion].**
- **The management of constipation should be individualised [Level of evidence - V; category of guideline - suggestion].**
- **Patients should be offered adequate privacy, and appropriate equipment (e.g. commode, foot stool), to promote defaecation [Level of evidence - V; category of guideline - suggestion].**
- **Lifestyle changes (e.g. dietary fibre, exercise) have a limited role in patients with advanced cancer [Level of evidence - V; category of guideline - suggestion].**
- **Reversible causes of constipation should be treated, and potential aggravating factors should be minimised [Level of evidence - V; category of guideline - suggestion].**
- **Conventional laxatives should be considered as first-line treatment in patients with functional constipation [Level of evidence - I; category of guideline - recommendation].**
- **Conventional laxatives should be considered as first-line treatment in patients with secondary constipation [Level of evidence - V; category of guideline - suggestion].**
- **If patients with functional constipation / secondary constipation do not respond to first-line conventional laxatives, then re-assess the patient and consider adding or switching to another conventional laxative or specialist medication (e.g. linaclotide, lubiprostone, prucalopride) [Level of evidence - V; category of guideline - suggestion].**
- **Peripherally-acting mu-opioid receptor antagonists (PAMORAs) should always be considered in patients with opioid-induced constipation [Level of evidence - I; category of guideline - recommendation].**
- **If patients with opioid-induced constipation do not respond to PAMORAs, then re-assess the patient and consider adding or switching to a conventional laxative or specialist medication (e.g. lubiprostone, prucalopride) [Level of evidence - V; category of guideline - suggestion].**
- **Patients prescribed opioid analgesics should be routinely co-prescribed laxatives *(or a PAMORA)* [Level of evidence - IV; category of guideline - suggestion].**

- **Suppositories / enemas should only be used in patients with evidence of stool in the rectum and / or descending colon that have not responded to other interventions [Level of evidence - V; category of guideline - suggestion].**
- **Other interventions should generally only be used in patients with "resistant" constipation [Level of evidence - V; category of guideline - suggestion].**
- **All patients with constipation should be regularly re-assessed [Level of evidence - V; category of guideline - suggestion].**
- **Patients with ongoing "resistant" constipation should be referred to a specialist for further investigation / management [Level of evidence - V; category of guideline - suggestion].**

Table 1 – Recommendations for management of constipation in patients with advanced cancer.

Rome IV criteria for functional constipation	Rome IV criteria for opioid-induced constipation
1. Must include 2 or more of the following: a) Straining during more than one-fourth (25%) of defecations b) Lumpy or hard stools (BSFS 1-2) more than one-fourth (25%) of defecations c) Sensation of incomplete evacuation more than one-fourth (25%) of defecations d) Sensation of anorectal obstruction / blockage more than one-fourth (25%) of defecations e) Manual maneuvers to facilitate more than one-fourth (25%) of defecations (e.g. digital evacuation, support of pelvic floor) f) Fewer than 3 spontaneous bowel movements per week 2. Loose stools are rarely present without the use of laxatives 3. Insufficient criteria for irritable bowel syndrome Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.	1. New or worsening symptoms of constipation when initiating, changing, or increasing opioid therapy that must include 2 or more of the following: a) Straining during more than one-fourth (25%) of defecations b) Lumpy or hard stools (BSFS 1-2) more than one-fourth (25%) of defecations c) Sensation of incomplete evacuation more than one-fourth (25%) of defecations d) Sensation of anorectal obstruction / blockage more than one-fourth (25%) of defecations e) Manual maneuvers to facilitate more than one-fourth (25%) of defecations (e.g. digital evacuation, support of pelvic floor) f) Fewer than 3 spontaneous bowel movements per week 2. Loose stools are rarely present without the use of laxatives

Table 2 - Rome IV diagnostic criteria for functional constipation and opioid-induced constipation [9].

CATEGORY	EXAMPLES
Laxatives Bulk-forming laxatives	▪ Ispaghula husk (oral) ▪ Methylcellulose (oral) ▪ Sterculia (oral) ▪ Sterculia with frangula (oral)
Osmotic laxatives	▪ Lactulose (oral) ▪ Macrogol 3350 with potassium chloride, sodium bicarbonate and sodium chloride (oral) ▪ Magnesium hydroxide (oral) ▪ Sodium acid phosphate with sodium phosphate (oral, enema)
Softening laxatives	▪ Aracus oil (enema) ▪ Docusate sodium (oral, enema) ▪ Liquid paraffin (oral) ▪ Liquid paraffin with magnesium hydroxide (oral)
Stimulant laxatives	▪ Bisacodyl (oral, enema, suppository) ▪ Co-danthramer (oral) ▪ Co-danthrusate (oral) ▪ Glycerol (suppository) ▪ Senna (oral) ▪ Senna with ispaghula husk (oral) ▪ Sodium picosulfate (oral)
Other drugs Chloride-channel agonists	▪ Lubiprostone (oral)
Selective 5-HT_4 receptor agonists	▪ Prucalopride (oral)
Opioid receptor antagonists	▪ Methylnaltrexone (subcutaneous) ▪ Naloxegol (oral)
Bowel cleansing preparations	▪ Citric acid with magnesium carbonate (oral) ▪ Macrogol 3350 with anhydrous sodium sulfate, ascorbic acid, potassium chloride, sodium ascorbate and sodium chloride (oral) ▪ Macrogol 3350 with anhydrous sodium sulfate, potassium chloride, sodium bicarbonate and sodium chloride (oral) ▪ Magnesium citrate with sodium picosulfate (oral) ▪ Bisacodyl (oral and suppository) ▪ Docusate sodium (oral, enema) ▪ Magnesium sulfate (oral)

Table 3 – Drugs used to treat constipation [adapted from reference 43].