Care Management Guidelines

Nausea and Vomiting
Nausea and Vomiting

Introduction
- Nausea and vomiting are common symptoms in patients with advanced and incurable diseases, especially cancer (40-70%).
- Even low-grade nausea is an unpleasant and debilitating symptom as any one who has experienced travel sickness will confirm, so active palliative management is important and urgent.
- Identification and treatment of a principal underlying cause may abolish the symptoms, but symptomatic management with anti-emetic drugs, is almost always necessary regardless of cause, especially initially.

Key Principles
- Nausea and vomiting result from the activation of protective physiological mechanisms that exist in order to eliminate toxins from the body. Therefore an understanding pathophysiology and pharmacology are fundamental to management.
- Impaired gastric emptying is a common and underestimated cause of nausea and vomiting.
- Obstruction and gastric outflow impairment may not respond to drugs alone and mechanical (surgical) interventions may be the only means of symptom relief.
- Non-pharmacological interventions and the influence of psychological factors always need to be considered.
- Pre-emptive treatment should be considered in situations where nausea and vomiting may be expected, such as the commencement of opioids, and before, during or after chemotherapy and radiotherapy.

Assessment
- A cause should be sought by clinical means, and, where appropriate, by investigation. Causation may be multi-factorial, and sometimes no cause is identified.
- Differentiation between obstructive and non-obstructive causes is essential. Malignant bowel obstruction (MBO) is often missed in its early or sub-total presentations.

History
- Teasing out what a patient means when they say 'I feel sick' will provide valuable information about the underlying mechanism that is causing the nausea and vomiting.
- Nausea can be a difficult symptom to describe. It may be accompanied or followed by dry reaching (or retching), and then by outright vomiting. Sometimes vomiting may occur without preceding nausea.
- A targeted history is needed including:
  - full drug and cancer treatment history;
  - presence or absence of flatus;
  - colic;
  - bowel history.
Useful Questions When Assessing Nausea and Vomiting

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<tr>
<th>Onset: When did it begin? How often does it occur? Does nausea always occur before the vomiting? Is nausea always present?</th>
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<tbody>
<tr>
<td>• <strong>Provocation/ameliorating factors:</strong> What brings it on? (smells, food, eating, medications, anxiety, movement) What makes it better? (medication, vomiting, relaxation) What makes it worse?</td>
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<td>• <strong>Key question:</strong> does vomiting relieve (partially or completely) the nausea? If yes, strongly consider an obstructive cause. If no, consider chemical (Chemoreceptor trigger zone - CTZ) causes.</td>
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<td>• <strong>Quality:</strong> What does it feel like? Can you describe it? Is it associated with abdominal pain, bloating, vertigo (rotational dizziness), headache or any other symptoms?</td>
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<td>• <strong>How intense are these feelings?</strong> (on a scale of 0 to 10) At their worst? At best? Right now? On average? How bothered are you by these symptoms?</td>
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<td>• <strong>Effect of treatments:</strong> What medications and treatments are you currently using? How effective are these? Any side-effects? What have you tried in the past for this?</td>
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The following features suggest high obstruction/gastric outflow obstruction:
- epigastric discomfort, fullness, early satiety, flatulence, hiccup, acid reflux
- cycles of increasing nausea relieved by vomiting (often large volume and faeculent), gradually filling up again, satiety, nausea, and then vomiting again.

**Examination**
- Hydration status, state of mouth, tongue and teeth.
- Abdominal palpation, auscultation.
- Rectal examination - look for rectal impaction and the signs of high constipation with or without overflow (so-called ‘spurious’ diarrhoea): ‘ballooned’ empty rectum, faecal incontinence, foul faecal matter on the glove.

**Investigation**
- Urea and electrolytes, liver function tests and calcium.
- Abdominal x-ray (supine, and erect if obstructive cause suspected), also useful for assessing severe symptomatic constipation.
- Abdominal CT (for suspected MBO).
- Contrast studies of upper or lower GI tract are occasionally useful to delineate functional issues.

**Pathophysiology**
- The principal sites of pathway activation are:
  - gastrointestinal tract, either stasis or irritation of the mucosa;
  - chemoreceptor Trigger Zone (CTZ) in the base of the fourth ventricle;
  - vestibular apparatus;
  - cerebral cortex.
- These areas stimulate the vomiting centre in the brainstem that coordinates the act of vomiting via autonomic efferents to the upper gastrointestinal tract, diaphragm and abdominal muscles.
• The primary neurotransmitters involved are dopamine, serotonin, acetylcholine, and histamine.

Causes

Mediated by effects on the gastrointestinal tract
Gastro-intestinal transit time tends to be increased in patients with advanced cancer, particularly if receiving opioids. Delayed gastric emptying may be a significant contributory cause; Prevention and treatment of constipation are always necessary.

• Gastric outflow obstruction:
  o obstruction (partial or complete);
  o mass effect (hepatic or other tumour mass, carcinomatosis);
  o constipation (Constipation may still be present despite poor intake and presence of bowel motions).
• Gastric mucosal inflammation (NSAIDs, steroids, antibiotics, blood, ethanol, stress);
• Gastric stasis;
• Vagal stimulation;
• Oesophageal causes: extrinsic or intrinsic compression, mucosal inflammation due to reflux, or infections such as candidiasis or herpes simplex.

Mediated by chemical mechanism (usually via CTZ)

• Drugs:
  o commonest pharmacological cause in palliative care practice is opioids, usually after commencing in an opioid-naïve patient, or after dose escalation.
  o others: many drugs cause nausea, but antibiotics and anticonvulsants are particularly common.
  o cancer treatment: chemotherapy and radiotherapy.
• Biochemical
  o hypercalcaemia;
  o uraemia;
  o liver failure.
• Toxins (tumour factors, infection)

CNS

• Raised intracranial pressure (brain metastases, leptomeningeal disease, bleeding)

Vestibular

• Motion sickness
• Cerebellar tumour

In unexplained nausea and vomiting:

• Opioid drugs should be reviewed as a potential cause and dose reduction or opioid substitution undertaken where appropriate;
• Raised intracranial pressure may be the cause due to brain metastases or leptomeningeal spread;
• Hypercalcaemia can occur in any malignancy and in the absence of bone disease;
• Undiagnosed renal or hepatic failure should be considered.
Management

Goals of Management

- Identify and treat reversible causes whenever possible;
- Stop or significantly reduce the vomiting;
- Re-hydrate the patient;
- Abolish nausea;
- Restore appetite and oral intake, where possible.

Principles of Medication Management

- Anti-emetic drug class choice should be based in theory on an understanding of pathophysiology (cause of the symptoms), and hence the relevant physiological pathways, receptor systems, and sites of drug action. However, in practice it is often a case of trying different agents alone or in combination and determining response.
- Regular anti-emetic drug therapy is necessary, achieving steady state plasma drug levels and maintaining them.
- Sometimes a combination of more than one anti-emetic drug class is necessary.
- As the final common pathway of prokinetic drugs is cholinergic, avoid using prokinetic and anticholinergic drugs simultaneously.
- Oral medications are ineffective if the patient is vomiting, and a subcutaneous infusion is then indicated. It is wise to have a low threshold for the early, and often temporary, use of a subcutaneous infusion for nausea and vomiting. The presence or absence of an element of obstruction is important in drug choice and management.
- If nausea and vomiting is actually regurgitation due to upper GIT obstruction, it will not respond well to anti-emetics.
- Prokinetic agents may be used in the presence of obstructive symptoms provided that colic is not present, especially where gastric stasis or partial outflow obstruction may be present. It has been widely taught that this is not advisable because of the risk of provoking colic, but local experience has not found this to be a common problem.

Prescribing

For further drug prescription information see Formulary, and web link resources.

- Choose first line antiemetic for obstructive or non-obstructive cause (bearing in mind that gastric stasis is probably very common).
- Except when symptoms very mild and intermittent, give drugs regularly.
- Choose appropriate route of administration (if vomiting use subcutaneous route, at least initially).
- Prescribe a top-up dose schedule.
- If nausea or vomiting persist, review.
- Consider second line agent.
- Not all nausea and vomiting-type symptoms respond to anti-emetics:
  - If nausea and vomiting is actually regurgitation due to upper GIT obstruction, it will not respond well to anti-emetics.
  - Pharyngeal stimulation by copious sputum is often overlooked as a cause of nausea and vomiting.
First Line Antiemetics

Prokinetic antiemetic
For gastric stasis and functional outflow obstruction:

• Metoclopramide
  o Pro-kinetic action on GIT
  o Reasonably good activity at CTZ (D₂ antagonist, weak 5HT₃ antagonist)
  o For gastric irritation, gastric stasis, functional bowel obstruction (peristaltic failure)
  o Mild to moderate opioid-induced nausea and/or vomiting, especially at onset of treatment:
    ▪ 10-20mg qid, po or sc
    ▪ 20-100mg/24 hours by continuous subcutaneous infusion (CSCI) via syringe driver

CTZ-targeting antiemetic for chemical causes
For most 'chemical' causes of nausea and vomiting (eg drugs, biochemical/metabolic causes, organ failure, tumour-produced toxins).

• Haloperidol (D₂ antagonist)
  o Potent dopaminergic blocking activity mainly at CTZ
    ▪ 0.5-3mg nocte or bd, po or sc
    ▪ 2.5-10mg/24 hours by CSCI

Vomiting centre-targeting antiemetic
For mechanical bowel obstruction, raised intracranial pressure, motion sickness.

• Phenergan (antihistamine, H₁ blocker)
  o antihistamine, H₁ blocker
  o PBS listed
  o Good for vestibular causes, motion sickness
    ▪ 25mg prn 4-6hrly.

• Prochlorperazine (D₂, H₁ antagonist, weak anti muscarinic)
  o Anticholinergic and vestibular effects
  o Irritant to tissues so cannot be infused subcutaneously
  o Parkinsonism-like effects common in prolonged use, so short term use only
    ▪ 10mg tablets 6hrly
    ▪ 25mg suppositories 6-8 hrly

Second Line Antiemetics

• Dexamethsone
  o Potent steroid.
  o Reduces peri-tumoral oedema:
    ▪ first-line in treatment of raised intracranial pressure;
    ▪ has been extensively used in early/subacute bowel obstruction (but evidence for efficacy uncertain).
  o Possible other central actions, so used in addition to other standard antiemetics, especially in chemotherapy-induced nausea and vomiting.
- 4mg qid, po; 16mg/24hrs usual ceiling dose, and titrate downwards depending on response. Long half-life, so can give once or twice a day. Morning administration advised to avoid sleep disturbance but evidence for this lacking.
- Can be infused subcutaneously.

- **Cyclizine** (Histamine H₁ antagonist, anti muscarinic)
  - Acts mainly directly on the vomiting centre.
  - For mechanical bowel obstruction, raised intra-cranial pressure (usually with dexamethasone), motion sickness/vestibular causes, pharyngeal stimulation.
  - A very widely used agent in palliative care practice overseas, but only available via Special Access Scheme (talk to palliative care service, local or hospital pharmacist).
- 25-50mg tds, po or sc
- 100-150mg/24 hours by CSCI

- **Methotrimeprazine** (Levomepromazine) (H₁, 5HT², D², anti muscarinic)
  - Broad spectrum of activity at a range of receptor sites
  - Useful if cause of nausea and vomiting unclear or multiple receptors/mechanisms implicated
  - Sedating so start with low doses
  - Beware of postural hypotension
  - Also useful in terminal restlessness/agitation (up to 50-75mg/24 hours by CSCI)
- 6.25-12.5mg nocté or bd, po or sc
- up to 25mg/24 hours by CSCI.

- **Ondansetron** (and Tropisetron, Granisetron) (5HT³ antagonists)
  - Block the effect of the release of serotonin by enterochromaffin cells in gut wall, caused by certain chemotherapy drugs or abdominal radiotherapy: therefore usefulness is usually restricted to these specific situations eg:
    - 8mg IV or 24mg orally 30mins before chemotherapy, 4-8mg 12hrly maintenance.
  - **Note:** These drugs cause significant constipation.

**Other Medications**

- Benzodiazepines: for anxiety-related causes eg:
  - **lorazepam** 0.5-1mg po or s/l, bd or tds.
  - **oxazepam** 15-30mg po, bd

- Antisecretory drugs: in bowel obstruction with copious, high volume vomiting eg:
  - **Hyoscine Butylbutomide** (*Buscopan*)
    - Muscarinic anticholinergic agent
    - Does not cross blood-brain barrier so no central sedation
    - Smooth muscle relaxant and secretion reduction
    - Also treats colicky pain, terminal secretions
    - 20mg 6hrly, po
    - 20-40mgs IV/sc stat, repeat after 30mins if needed.
    - 60-120mg/24hrs by CSCI (max reported, 300mg/24hrs).

- **Octreotide**
  - synthetic hormone (somatostatin analogue);
100-200 micrograms bd, sc
600-1200 micrograms/24hrs by CSCI.

**Failure to Respond to Anti Emetics**
Consider:
- multiple mechanisms
- inadequate dose
- poor absorption
- incomplete or wrong diagnosis
- poor compliance
- recognised emotional/psychological factors.

**Malignant Bowel Obstruction (MBO)**
Malignant bowel obstruction (MBO) is often less clear-cut than other causes of bowel obstruction. It may be incomplete and intermittent, with spontaneous remission. The bowel lumen may be occluded or not, sometimes a pseudo-obstructive picture is seen, and may have neuropathic, endocrine and/or vascular causes.
- Malignancies causing bowel obstruction:
  - ovary
  - colorectal
  - stomach
  - breast, lung, melanoma, lymphoma (unusual but well described)
  - can rarely occur with many tumours
- Pseudo-obstruction:
  - Obstructive symptoms and signs without demonstrable mechanical site(s) of bowel lumen occlusion
  - ileus picture
  - Maybe due to physiological, neurogenic or vascular disruption
  - Causes:
    - abdominal carcinomatosis
    - constipation
    - drugs (opioids)
    - unknown

**Management**
- **Analgesia:** patients will usually require low dose opioids even when the pain is not a prominent symptom.
- **Anti-emetics.**
- Parenteral route (via CSCI using syringe driver); eg (for opioid-naive patient) morphine 20mg/24hrs, metoclopramide 20mg/24hrs, +/- haloperidol 2.5mg/24hrs
- Also prescribe 'breakthrough' analgesia and anti-emetic eg initial doses of:
  - morphine 2.5-5mg prn
  - metoclopramide 10mg sc 6-8 hrly to a maximum total of 60mg/24 hrs (be particularly alert for extra pyramidal effects at doses > 30mg/24 hours)
  - haloperidol 0.5-1mg sc tds prn
• Hydration:
  o Intravenous route for inpatients;
  o Use hypodermoclysis (subcutaneous) infusion (S.C. fluids) at home or palliative care unit:
    ▪ 1 to 1.5 litres per day;
    ▪ normal saline;
    ▪ NOT in limbs or oedematous areas.
• Consult original surgeon or gynaecologist if possible.
• An inpatient admission may be necessary to treat an episode of MBO.
• Shared care with a surgeon may be recommended (preferably the original surgeon or one with a special interest, eg upper GI). Decompressive or bypass surgery, and palliative venting gastrostomy may be potentially effective options to consider.
• Two-tiered decision-making is recommended:
  (Q1) what is the best way to relieve this symptom?
  (Q2) is it appropriate to recommend to this patient at this time?
  Do not rule anything out on basis of prognosis until alternatives have been explored.
• Consider mechanical decompression (see below).
• Wait and see if spontaneous resolution occurs.
• Diagnostic passage of nasogastric tube may be necessary, also may clear large ‘sump’ volume in upper GI tract.
  **Note:** Some patients may elect to retain the nasogastric tube while it is draining and relieving symptoms.
• Relieve obstruction, by surgery if possible and appropriate:
  o Bypass/decompression (minimally invasive approach if possible)
  o Palliative venting gastrostomy
• Gastric and oesophageal mucosal inflammation are very common in MBO.
• Gastrograffin swallow may be therapeutic in MBO.

**Nursing Management**

• Explanation and reassurance about the possible causes, about investigations and treatments that may be necessary.
• **Odour:** avoid strong smells (eg food, infected/necrotic tumours etc); use of deodorisers.
• **Environment:** space, air movement
• Dietary interventions:
  o small amounts of food more frequently;
  o cold rather than hot food;
  o avoid spicy, rich, fatty and very sweet food ;
  o salty food tends to be tolerated better eg dry biscuits;
  o small frequent drinks or sips of fluid;
  o crushed ice cubes / frozen drinks such as coke, fruit juice.
  o ginger is a useful known antiemetic, in ginger tea or crystalline form.
• Good oral hygiene (especially after vomits);
• Relaxation / distraction techniques ;
• Acupuncture and hypnosis may have a role for practitioners who have these skills;
• Position: sitting upright, raised head of bed to relieve pressure on abdomen;
• Relaxation therapy.

**Consultation and Advice**

Consider seeking advice:
• When there is an obstruction;
• Opioid-induced nausea and vomiting; or
• Failure to respond to first line anti-emetics.

**Contact details**

Palliative Care South
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