Anorexia, cachexia, nausea and vomiting

Robert Twycross

What's new ?

- Low-dose levomepromazine, 6–25 mg/24 hours, has become more widely used and in some centres is prescribed before hyoscine butylbromide in inoperable chronically obstructed patients
- Although not available as an injection, olanzapine has been used in patienst with refractory nausea and vomiting, particularly when the much cheaper levomepromazine causes unacceptable sedation

Anorexia, cachexia, nausea and vomiting are common in advanced cancer. Although evidence from randomized controlled trials is limited, a rational approach to management is possible provided the doctor is:

- aware of the common causes
- able to work from basic knowledge of anatomy, physiology and pharmacology.

Anorexia

Anorexia may be primary (as in cachexia–anorexia syndrome) or secondary to one or more other conditions (Figure 1). Although anorexia and early satiety are often linked, early satiety also occurs without concomitant anorexia (*"Although I look forward to my meals, I feel full up after a few mouthfuls and can't eat any more"*). Early satiety without anorexia is associated with a small stomach (post-gastrectomy), gastric stasis, hepatomegaly and gross ascites. Patients are often more accepting of anorexia than their families.

Management – helping the patient and family accept and adjust to reduced appetite is often the focus of management.

- Listen to the family's fears.
- Explain to the family that, in the circumstances, it is normal to be satisfied with less food; and with a fickle appetite they can help by providing food when the patient is hungry (a microwave oven is useful).
- A small helping looks better on a smaller plate.
- Offer specific dietary advice, particularly for patients with early satiety.
- Lightly spiced food helps taste, and mild alcohol (e.g. wine) moistens food.
- Discourage the 'he-must-eat-or-he-will-die syndrome' by emphasizing that a balanced diet is unnecessary at this stage in the illness (*"Just give little of what he fancies", "I shall be happy even if he just takes fluids"*).
- Recognize the 'food-as-love' and 'feeding-him-is-my-job' syndromes, and use them as an opportunity to discuss the progressive impact of the illness with the spouse/partner.
- Eating is a social habit, and people generally eat better at a table and when dressed.

Appetite stimulants are helpful in some patients. They should be stopped if no benefit is seen after 1 week. A corticosteroid (e.g. prednisolone, 15–30 mg o.d., dexamethasone, 2–4 mg o.d.) is sometimes useful, but the effect may last only a few weeks. A progestogen (e.g. medroxyprogesterone acetate, 400 mg o.d., megestrol, 160 mg o.d.) may have an effect lasting months and is generally associated with weight gain.

Appetite stimulants are inappropriate in patients with early satiety without concurrent anorexia.

Causes of poor appetite in advanced cancer

Causes	Management possibilities
• Unappetizing food	Choice of food by patient
• Too much food provided	Small meals
• Altered taste	Adjust diet to counter taste changes
• Dyspepsia	Antacid, antiflatulent, prokinetic drug
• Nausea and vomiting	Anti-emetics
• Early satiety • Fatigue	'Small and often', snacks rather than meals
• Gastric stasis	Prokinetic drug
• Constipation	Laxative
• Sore mouth	Mouth care
• Pain	Analgesics
• Malodour	Treatment of malodour
• Biochemical	
Hypercalcaemia	Correct hypercalcaemia
Hyponatraemia	Demeclocycline, 300mg b.d. to q.d.s., if caused by syndrome of inappropriate antidiuretic hormone secretion
Uraemia	Anti-emetic
• Secondary to treatment	
Drugs	Modify drug regimen
Radiotherapy Chemotherapy	Anti-emetic
• Disease process	Appetite stimulant
• Anxiety	Anxiolytic
• Depression	Antidepressant

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Cachexia

Cachexia (marked weight loss and muscle wasting) is generally associated with anorexia. It is a paraneoplastic phenomenon that is exacerbated by various factors (Figure 2) and occurs in more than 80% of patients with advanced cancer. The incidence is highest in gastrointestinal and lung cancers. It may antedate the clinical diagnosis, and can occur in patients with a small primary neoplasm. Cytokine production suggests a chronic inflammatory component and explains the beneficial effect of non-steroidal anti-inflammatory drugs (NSAIDs) in some patients.

Clinical features – the principal features of cachexia–anorexia syndrome are:

- marked weight loss
- anorexia
- weakness
- fatigue.

Associated physical features include altered taste, loose dentures causing pain and difficulty eating, pallor (anaemia), oedema (hypoalbuminaemia) and decubitus ulcers. Psychosocial consequences include ill-fitting clothes (increased feelings of loss and displacement), altered appearance (engenders fear and isolation), and difficulties in social and family relationships.

Management – efforts should aimed at ameliorating the social consequences and physical complications.

- Do not weigh the patient routinely.
- Educate the patient and family about the risk of decubitus ulcers and the importance of skin care.
- If affordable, encourage the patient to buy new clothes to enhance self-esteem.
- Reline dentures to improve chewing and facial appearance; as a temporary measure, this can be undertaken at the bedside and lasts about 3 months.
- Supply equipment to help maintain personal independence (e.g. raised toilet seat, commode, walking frame, wheelchair).

Aggressive dietary supplementation via a nasogastric tube or intravenous hyperalimentation is of little value in reversing cachexia in advanced cancer because of the increased metabolic rate and abnormal metabolism. However, dietary advice is important, particularly if there are associated changes in taste. Some patients benefit psychologically from powdered or liquid nutritional supplements, and a few gain weight.

A trial of therapy with an appetite stimulant may help some patients. However, progestogens are expensive and should be used selectively. The effect of progestogens may be enhanced by concurrent use of ibuprofen, 1200 mg/day, or another NSAID.

Nausea and vomiting

Gastric stasis, intestinal obstruction, drugs and biochemical factors account for most cases of nausea and vomiting in advanced cancer; raised intracranial pressure accounts for less than 5%. It is important to identify the most likely cause in each patient, because treatment depends on the cause. On the basis of putative sites of action, it is possible to determine the anti-emetic drug of choice in various situations (Figure 3). The initial choice is generally metoclopramide, haloperidol, hyoscine butylbromide (or glycopyrronium) or cyclizine (or dimenhydrinate or promethazine). Other drugs may be necessary in some patients.

Causes of cachexia in advanced cancer

Paraneoplastic

- Cytokines produced by host cells and tumour (e.g. tumour necrosis factor, interleukin-6, interleukin-1)
- Proteolysis-inducing factor → abnormal metabolism of protein, carbohydrate
- Altered fat metabolism
- Increased metabolic rate → increased energy expenditure
- Nitrogen trap by the tumour

Impaired oral intake

- Dry mouth (xerostomia)
- Sore mouth (stomatitis)
- Altered taste
- Dysphagia, odynophagia
- Nausea and vomiting
- Bowel obstruction
- Severe pain, dyspnoea
- Depression
- Cognitive impairment (delirium, dementia)
- Social and financial difficulties

Impaired gastrointestinal absorption

- Malabsorption
- Chronic diarrhoea
- Frequent drainage of ascites
- Loss of proteins
- Ulceration
- Haemorrhage or pleural effusion
- Nephrotic syndrome

Catabolic states

- Acute or chronic infection
- Hyperthyroidism

Debilitating treatment

- Surgery
- Radiotherapy
- Chemotherapy

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Corticosteroids are anti-emetics; they possibly act by reducing the permeability of the chemoreceptor trigger zone (area postrema) and of the blood–brain barrier to emetogenic substances, and by reducing the neuronal content of γ-aminobutyric acid (GABA) in the brain stem. Corticosteroids also reduce leu-enkephalin release in the brain stem and gastrointestinal tract.

Gastric stasis (delayed gastric emptying) accounts for about 25% of cases of nausea and vomiting.

Clinical features range from mild dyspepsia and anorexia to persistent severe nausea and large-volume vomiting (Figure 4). Gastric stasis is generally functional and is associated with one or more of the following conditions:

- dysmotility dyspepsia (often longstanding)
- constipation
- drugs (e.g. opioids, antimuscarinics, aluminium hydroxide, levodopa)
- cancer of the head of the pancreas (disrupts duodenal transit)

Management of nausea and vomiting in palliative care

1 After clinical evaluation, document the most likely cause of the nausea and vomiting in the patient's case notes (e.g. gastric stasis, intestinal obstruction, biochemical, drugs, raised intracranial pressure).
2 Ask the patient to record symptoms and response to treatment, preferably using a diary.
3 Correct correctable causes/exacerbating factors (e.g. drugs, severe pain, infection, cough, hypercalcaemia). Correction of hypercalcaemia is not always appropriate in dying patients. Anxiety exacerbates nausea and vomiting from any cause and may need specific treatment.
4 Prescribe the most appropriate anti-emetic stat, regularly and p.r.n. Give subcutaneously if continuous nausea or frequent vomiting, preferably by continuous subcutaneous infusion (CSCI).

Commonly used anti-emetics

Prokinetic anti-emetic (about 50% of prescriptions)
For gastritis, gastric stasis, functional bowel obstruction (peristaltic failure)

- Metoclopramide 10 mg p.o stat and q.d.s. or 10 mg s.c. stat and 40–100 mg/24hours CSCI, and 10 mg p.r.n. to q.d.s.

Anti-emetic acting principally in chemoreceptor trigger zone
(25% of prescriptions)
For most chemical causes of vomiting (e.g. morphine, hypercalcaemia, renal failure)

- Haloperidol 1.5–3mg p.o. stat and o.n. or 2.5–5 mg s.c. stat and 2.5–10 mg/24 hours CSCI, and 2.5–5 mg p.r.n. to q.d.s.
- Metoclopramide also has a central action

Antispasmodic and antisecretory anti-emetic
If bowel colic and/or need to reduce gastrointestinal secretions

- Hyoscine butylbromide, 20 mg s.c. stat, 80–200 mg/24 hours CSCI, and 20 mg s.c. hourly p.r.n.

Anti-emetic acting principally in the vomiting centre
For raised intracranial pressure (in conjunction with dexamethasone), motion sickness and in organic bowel obstruction

- Cyclizine, 50 mg p.o. stat and b.d.or t.d.s. or 50 mg s.c. stat and 100–150 mg/24 hous CSCI, and 50 mg p.r.n. to q.d.s.

Broad-spectrum anti-emetic
For organic bowel obstruction and when other anti-emetics are unsatisfactory

- Levomepromazine (methotrimeprazine), 6–12.5 mg p.o./s.c. stat, o.n. and p.r.n. to q.d.s.

5 Review anti-emetic dose every 24 hours, taking note of p.r.n. use and the patient's diary.
6 If there is little benefit despite optimization of the dose, has the correct cause been identified?
- If no, change to an alternative anti-emetic and optimize
- If yes, provided the anti-emetic has been optimized, add or substitute a second anti-emetic

7 Anti-emetics for inoperable bowel obstruction are best given by CSCI. Levomepromazine (methotrimeprazine) is the exception; it can be given as a single subcutaneous injection o.n.
Step 1 – metoclopramide[a] ± dexamethasone[b]
Step 2 – levomepromazine[c]
Step 3 – hyoscine butylbromide[d] + levomepromazine[c]
(a, if severe colic, move to step 3; b, use if only partial success with metoclopramide, aim is reduction in peritumour oedema; c, when levomepromazine is too sedative, consider substituting olanzapine (dispersible tablets), 1.25–2.5 mg o.d., or give cyclizine or haloperidol, or both; d, alternatively, use glycopyrronium, 600–1200 µg/24 hours)
8 In patients who fail to respond to the commonly used anti-emetics, consider the following.
- Corticosteroid (adjuvant anti-emetic for bowel obstruction and when all else fails) – dexamethasone, 8–16 mg p.o./s.c. stat and o.d.; consider reducing the dose after 7 days
- 5-HT3-receptor antagonist (use when massive release of 5HT from enterochromaffin cells or platelets, e.g. chemotherapy, abdominal radiation, bowel obstruction (distension), renal failure) – tropisetron, 5 mg p.o./s.c. stat and o.d.
- Somatostatin analogue (anti-secretory agent without antispasmodic effects; use in obstruction if hyoscine inadequate, either alone or in addition to hyoscine butylbromide, 120 mg/24hours CSCI) – octreotide, 100 µg stat, 250–500 µg/24 hours CSCI, and 100 µg p.r.n. to q.d.s.

9 Some patients with nausea and vomiting need more than one anti-emetic.
10 Antimuscarinic drugs block the cholinergic pathway through which prokinetics act; concurrent use antagonizes the prokinetic effect of metoclopramide and is best avoided.
11 Continue anti-emetics unless the cause is self-limiting.
12 Except in organic bowel obstruction, consider changing to p.o. after 72 hours of good control with CSCI.

- paraneoplastic autonomic neuropathy
- retroperitoneal disease (leads to neural dysfunction)
- spinal cord compression
- diabetic autonomic neuropathy.

Epigastric distension and/or a succussion splash may be found on examination. A succussion splash requires the presence of more than 400–500 ml of fluid in the stomach and plenty of gas. Other features are as follows.

- Bowel sounds are generally normal but may be reduced if the stasis is opioid-induced.
- Flatus ('downwind') is unaffected.
- Bowel habit is not directly affected.
- If gastric stasis is associated with autonomic neuropathy, there may be other detectable autonomic abnormalities (e.g. orthostatic hypotension without compensatory tachycardia).

Management centres on explanation and use of a prokinetic drug, preferably metoclopramide (Figure 5). This generally leads to improvement and resolution of any succussion splash.

Warning – antimuscarinic drugs bind to receptors on intestinal muscle fibres and competitively block the effect of prokinetic drugs. As a general rule, prokinetic and antimuscarinic drugs should not be prescribed concurrently. However, domperidone and metoclopramide continue to exert an antagonistic effect at dopamine type 2 receptors in the chemoreceptor trigger zone in the brain stem, even when their prokinetic effect on the upper gut has been blocked.

Gastric outflow obstruction: gastric stasis is sometimes associated with organic gastric outlet obstruction (cancer of the gastric antrum or external compression of the gastric antrum or duodenum by a tumour). This can cause major management difficulties. Each case needs individual evaluation and treatment. In most patients, the obstruction is incomplete – even without oral intake, the stomach needs to clear swallowed saliva (up to 1.5 litres/24 hours, but may be decreased by an antimuscarinic drug or dehydration) and basal gastric juices (about 1.5 litres/24 hours). Thus, if a patient is vomiting less than 2–3 litres/24 hours, something is passing the obstruction.

Management – the mainstay of management is generally an antisecretory drug. Hyoscine butylbromide, 80–120 mg/24 hours continuous s.c. infusion (CSCI), reduces gastric secretions by about one-half and reduces the volume of saliva, but this benefit is partly negated if the patient receives intravenous fluid. Hyoscine causes a dry mouth, which needs regular moistening. In the USA, where parenteral hyoscine butylbromide is unavailable, glycopyrronium, 800–1200 µg/24 hours, can be substituted.

H_2-receptor antagonists (e.g. cimetidine, ranitidine) reduce both the acid content and the volume of gastric secretions and may provide additional benefit. In contrast, proton pump inhibitors reduce gastric acid production but do not significantly reduce the volume of gastric secretions. Somatostatin analogues, which are antisecretory but not antispasmodic, are used in some centres (e.g. octreotide, 300–600 µg/24 hours) alone or in conjunction with hyoscine butylbromide. Cost is a limiting factor.

A venting procedure (nasogastric tube or gastrostomy) is seldom necessary.

Obstruction: bowel obstruction in advanced cancer may be caused by one or more of the following:

- the cancer
- previous treatment (e.g. adhesions, post-radiation ischaemic fibrosis)
- drugs (e.g. opioids, antimuscarinics)
- associated with debility (e.g. constipation)
- an unrelated benign condition (e.g. strangulated hernia).

Clinical features – in acute bowel obstruction, there is typically a single discrete lesion, whereas in chronic obstruction (persistent or remittent) there may be several sites of partial obstruction in both the small and the large bowel. Retroperitoneal disease may cause visceral neuropathy and functional obstruction. The quartet of symptoms and signs that indicate a diagnosis of acute intestinal obstruction (abdominal distension, pain, vomiting and

Clinical features of gastric stasis

Some or all of the following symptoms may occur

- Early satiety
- Belching
- Post-prandial fullness
- Hiccup
- Epigastric bloating
- Nausea
- Epigastric discomfort
- Retching
- Heartburn
- Vomiting

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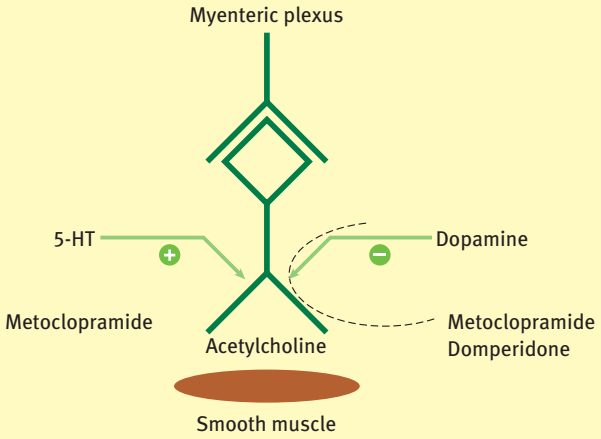
Post-ganglionic drug effects in gastric stasis



Metoclopramide, cisapride and domperidone affect gastroduodenal coordination via a post-ganglionic effect on cholinergic nerves from the myenteric plexus

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constipation) may not all be present in chronic obstruction in advanced cancer. For example, distension may be minimal because of multiple intra-abdominal malignant adhesions. Bowel sounds vary from absent to overactive with borborygmi (tinkling bowel sounds are unusual). Some patients have diarrhoea rather than constipation.

Surgical intervention should be considered when all of the following criteria are fulfilled.

- A single, discrete organic obstruction seems likely (e.g. post-operative adhesions, an isolated neoplasm).
- The patient's general condition is good (he does not have widely disseminated disease and has been independent and active).
- The patient is willing to undergo surgery.

The following are contraindications to surgical intervention:

- previous laparotomy findings preclude successful intervention
- intra-abdominal carcinomatosis (as shown by diffuse, palpable intra-abdominal tumours)
- massive ascites, re-accumulating rapidly after paracentesis.

In addition, weight loss of more than 9 kg is associated with a poor outcome after surgery.

Medical management – in patients in whom an operative approach is contraindicated, it is generally possible to relieve symptoms adequately with drugs (Figure 3). A nasogastric tube and intravenous hydration are seldom necessary. Management focuses primarily on the relief of nausea and vomiting. In patients without colic who continue to pass flatus, a prokinetic drug is the initial drug of choice. In patients with severe colic, prescribe an antisecretory and antispasmodic drug (e.g. hyoscine butylbromide, glycopyrronium).

Bulk-forming, osmotic and stimulant laxatives should also be stopped. A series of drug changes over several days may be necessary before optimum relief is achieved. Morphine or diamorphine should be given regularly for constant background cancer pain. In patients receiving parenteral metoclopramide or hyoscine butylbromide, the opioid can also be given by CSCI. A phosphate enema should be given if constipation is a probable contributory factor and a faecal softener prescribed (docusate sodium tablets, 100–200 mg b.d.).

Corticosteroids benefit some patients with inoperable intestinal obstruction. Because spontaneous resolution occurs in at least one-third of patients, it is important not to prescribe a corticosteroid too soon. Treat the symptoms as suggested above and then, after 5–7 days, if the obstruction has not settled, a trial of a corticosteroid for 3 days should be considered (e.g. dexamethasone, 8–16 mg s.c.). If there is improvement, either continue with the corticosteroid at a lower oral dose, or stop and review the need for long-term treatment.

Consider adding octreotide if vomiting is not reduced to once or twice daily by hyoscine butylbromide, 120–200 mg CSCI. Octreotide has an antisecretory effect throughout the alimentary tract. Octreotide can also be given by CSCI (e.g. 250–500 µg/24 hours, occasionally more). A reduction in intestinal contents reduces distension and thereby the likelihood of colic and vomiting.

A venting gastrostomy is seldom necessary for chronic obstruction in advanced cancer. Patients managed by drug therapy should be encouraged to drink and eat small amounts of their favourite beverages and food. Some patients find that they can tolerate food best in the morning.

Antimuscarinic drugs and reduced fluid intake result in a dry mouth and thirst. A few millilitres of fluid taken every 20–30 minutes, possibly as a small ice cube, is often helpful. Intravenous hydration is seldom needed. ◆

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Practice points

- Cancer-related anorexia and weight loss are often best managed by helping the patient and family to adjust to a largely irreversible situation
- Gastric stasis and bowel obstruction account for about one-half of cases of nausea and vomiting in advanced cancer
- Colic is the defining symptom in patients with obstruction; if it is mild or absent, prescribe a prokinetic drug (e.g. metoclopramide) – if it is severe, prescribe an antispasmodic (e.g. hyoscine butylbromide)
- If vomiting relieves nausea for several hours, the cause is likely to be gastric stasis or bowel obstruction; if it provides little or no relief, the cause is likely to be biochemical or drug stimulation of the chemoreceptor trigger zone