Taking care of the terminally ill cancer patient: management of gastrointestinal symptoms in patients with advanced cancer

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Introduction

The management of symptoms related to the gastrointestinal system is a major and ongoing challenge in the care of patients with advanced cancer. Symptoms such as constipation and anorexia are among the most common symptoms endured by patients. Their clinical significance derives not only from the direct consequences on patients’ comfort and function, but also from the perceived significance of the symptoms to the patients.

Management of gastrointestinal symptoms is predicated on careful assessment, particularly to identify remediable causes, and familiarity with a range of potentially effective therapeutic strategies.

Anorexia

Anorexia is defined as a decreased or poor appetite [1]. It is a very common problem among patients with advanced cancer. It must be differentiated from starvation, in which the patient has an appetite for food but is unable to eat or to tolerate food.

Potentially reversible causes

Patients should be evaluated for potentially reversible causes of anorexia that may be amenable to a specific intervention (Table 1).

Family anxiety

Since it is often the family who are concerned about the patient’s diminished oral intake rather than the patients themselves, it is crucial to ask who is experiencing or perceiving a problem, i.e. the patient or the concerned family members. Family members often need to be educated that terminally ill patients eat less, and that increasing caloric intake in cancer patients may not improve patient well being and that it may, indeed, ‘feed’ the cancer.

Non-medical interventions

Non-medical interventions include resting before meals (increased calories at breakfast when the patient is most rested), sitting upright for meals and optimizing aesthetics of food presentation. Pay attention to the patient’s likes and dislikes, and avoid foods with strong odours and tastes. Consider appetite stimulants, such as alcohol, caffeine or ginger ale, before meals.

Medical interventions

Megestrol acetate

This is the most widely used agent [2, 3]. It is effective in increasing both appetite and weight. Most of the weight gain is fat rather than muscle. The optimal dose is 360–480 mg/day orally [4]. Some patients respond to lower doses [4]. The most common adverse event is fluid retention, which may, occasionally, be severe. This may be a problem in patients with pre-existing effusions or edema.

Corticosteroids

In the short-term, corticosteroids may promote an enhanced feeling of well-being and improve appetite, food intake and performance status, but this effect is limited to ~4 weeks’ duration [3]. For patients with early-stage disease the adverse effects of long-term therapy may outweigh the potential benefits.

Dronabinol

The cannabinoid dronabinol has been associated with increased appetite and body weight [5]. It is less effective than megestrol acetate [6]. Side-effects of mild-to-moderate euphoria and dizziness are common, and may be problematic for some patients.

Prokinetic medications

Prokinetic medications such as metoclopramide can help with symptoms of anorexia related to early satiety [1, 7].

Enteral nutrition

Enteral nutrition is usually reserved for patients unable to swallow or for patients with gastric outlet obstruction when it may be provided by a feeding gastrostomy or jejunostomy, respectively [8–10]. Enteral nutrition improves nutritional status for patients with a starvation syndrome (who are unable to eat), but its effect on cachexia is minimal [11]. The rate of nutrient administration should be appropriate to avoid reflux and aspiration or fluid overload (particularly solute overload), which may precipitate diarrhea.
**Parenteral nutrition**

Total parenteral nutrition is not generally indicated for cancer cachexia. In uncommon situations in which patients with slowly progressive cancers are unable to eat or to derive benefit from enteral nutrition because of bowel obstruction or short bowel syndrome, total parenteral nutrition may be an appropriate option [12].

**Dry and sore mouth**

Xerostomia is a common symptom in patients with advanced cancer. As well as being distressing in itself, it also impairs swallowing, causes halitosis, reduces taste and food enjoyment, induces infection and caries, and may interfere with talking.

**Contributing factors**

Xerostomia is very common after radiation therapy to the head and neck region, which affects the function of salivary glands in the radiation field. Medications with anticholinergic effects such as the tricyclic antidepressants and opioids are common causes. Patients should be evaluated for evidence of oral candidiasis, mucositis or ill-fitting dentures. If any of these are present, they must be addressed.

**Management**

Providing oral hygiene at least twice a day is helpful. Other simple strategies include frequent mouth rinsing, chewing gum, using citrus-based lozenges, and consuming ice chips. In general, acidic or spicy foods may exacerbate symptoms and should be avoided [13, 14]. Artificial saliva, usually with a glycerin base, may relieve dry mouth. Pilocarpine 5 mg orally three times per day may stimulate salivation [14].

**Nausea and vomiting**

Nausea and vomiting are very common symptoms among patients with advanced cancer [15]. The management of this symptom is often challenging and complex.

**Contributing factors**

Many factors may contribute to these symptoms, and patients must be evaluated for potentially reversible causes of nausea and vomiting [15] (Table 2). Often patients may have multiple contributing factors. Where appropriate, specific interventions should be undertaken.

**General management**

Patients with established vomiting should be evaluated for signs of dehydration. They will often require intravenous hydration and parenteral (intravenous) or rectal antiemetics. Patients should be provided an appropriate sized bowl, tissues to wipe the mouth and water or juice to rinse the mouth. Nasogastric suction should be reserved for proximal gastrointestinal obstruction, particularly if there is evidence of feculent vomiting, to reduce odour.

### Table 1. Potentially reversible contributing factors contributing to anorexia

<table>
<thead>
<tr>
<th>Cause</th>
<th>Treatment option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered taste</td>
<td>Patient choice in foods</td>
</tr>
<tr>
<td>Early satiation</td>
<td>Smaller and more frequent meals</td>
</tr>
<tr>
<td>Constipation</td>
<td>Laxatives</td>
</tr>
<tr>
<td>Pain</td>
<td>Analgesia</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Rest</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>Bisphosphonates + hydration</td>
</tr>
<tr>
<td>Uremia</td>
<td>Specific treatment</td>
</tr>
<tr>
<td>Hepatic capsular distension</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Drugs</td>
<td>Discontinue or substitute</td>
</tr>
<tr>
<td>Depression</td>
<td>Antidepressant</td>
</tr>
</tbody>
</table>

### Table 2. Potentially treatable causes of nausea and vomiting

<table>
<thead>
<tr>
<th>Cause</th>
<th>Potential treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
</tr>
<tr>
<td>Gastric irritation</td>
<td>Stop NSAID, anti-ulcer medication</td>
</tr>
<tr>
<td>Gastric stasis</td>
<td>Nasogastric tube, prokinetic</td>
</tr>
<tr>
<td>Proximal gastrointestinal obstruction</td>
<td>Nasogastric tube or gastrostomy,</td>
</tr>
<tr>
<td></td>
<td>relieve obstruction (stent or bypass)</td>
</tr>
<tr>
<td>Ascites</td>
<td>Drain ascites</td>
</tr>
<tr>
<td>Hepatic capsular distension</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Severe constipation</td>
<td>Laxative, enema</td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td></td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>Hydration, bisphosphonates</td>
</tr>
<tr>
<td>Uremia</td>
<td>Hydration, treat specific cause,</td>
</tr>
<tr>
<td></td>
<td>haloperidol</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Candida esophagitis</td>
<td>Anti-fungal medication</td>
</tr>
<tr>
<td><strong>Drug-induced</strong></td>
<td></td>
</tr>
<tr>
<td>Opoids</td>
<td>Antiemetics, consider opioid</td>
</tr>
<tr>
<td></td>
<td>rotation</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Reduce dose</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td>Antiemetics: 5-HT, antagonist,</td>
</tr>
<tr>
<td></td>
<td>dexamethasone</td>
</tr>
<tr>
<td><strong>Antibiotics</strong></td>
<td>Antiemetics, switch antibiotic if</td>
</tr>
<tr>
<td></td>
<td>possible</td>
</tr>
<tr>
<td>Theophyllin</td>
<td>Reduce dose</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Mucosal protectant, cyclooxygenase-2-</td>
</tr>
<tr>
<td></td>
<td>specific NSAID</td>
</tr>
<tr>
<td>Iron supplements</td>
<td>Stop iron supplement</td>
</tr>
<tr>
<td><strong>Central nervous system</strong></td>
<td></td>
</tr>
<tr>
<td>Raised intracranial pressure</td>
<td>Dexamethasone, radiotherapy,</td>
</tr>
<tr>
<td></td>
<td>resection</td>
</tr>
<tr>
<td>Carcinomatosis meningitis</td>
<td>Dexamethasone, radiotherapy</td>
</tr>
</tbody>
</table>

NSAID, non-steroidal anti-inflammatory drug; 5-HT₃, 5-hydroxytryptamine-3.
**Cause-specific management**

Specific causes should be addressed (Table 2). Rational anti-emetic pharmacotherapy may involve a range of agents [16] (Table 3). In many cases, patients may need drug combination or sequential trials of agents until an appropriate remedy is identified [16].

**Constipation**

Constipation is common among patients with advanced cancer because of decreased mobility and fluid intake, but is perhaps most often related to medications in particular opioids, 5-hydroxytryptamine-3 (5-HT₃) antagonists and vinca alkaloids [17]. Importantly, constipation is often the first sign of a bowel obstruction.

**Evaluation**

Owing to the wide variability in normal bowel movement patterns in individual patients, the diagnosis of constipation can only be made in comparison with an individual’s normal pattern. Common subjective symptoms include a feeling of incomplete evacuation, bloating, decreased appetite, or generalized abdominal discomfort or pain. Physical examination should include the abdominal examination (distension, firmness, tenderness, the presence or absence of bowel sounds) and a rectal examination. Plain abdominal X-ray can help differentiate between constipation and bowel obstruction, and is the best way to evaluate the degree of constipation. Possibly reversible causes need to be considered and evaluated (Table 4).

**Laxatives**

Daily laxatives are indicated in any patient receiving opioid therapy [18] (Table 5). There are no data to indicate superiority of any one laxative approach. Many experienced clinicians suggest that the best relief with the lowest medication volume and incidence of adverse effects is obtained by the combination of a softening and stimulant agent (e.g. docusate and casanthranol, or docusate and senna). Purely bulk-forming agents, such as methylcellulose and psyllium, are not generally recommended because their safe use requires that they be taken with a large volume of fluid, otherwise they may form concretions and lead to impaction.
Bowel obstruction is a common problem in patients with terminal cancer, particularly with genitourinary or gastrointestinal malignant disease. Up to 42% of patients with ovarian cancer have bowel obstruction at the end of life.

Causes
Malignant bowel obstruction is commonly a result of intra-abdominal tumor masses or diffuse carcinomatosis causing intrinsic or extrinsic occlusion of the intestinal lumen, or intestinal motility disorders producing pseudo-obstruction. Paraneoplastic effects on the enteric nervous system have also been described.

Role of surgery
The initial approach to assess and manage malignant bowel obstruction in the advanced cancer patient involves determining whether the obstruction is reversible or not, and whether the obstruction is partial or complete. Suitability for surgery such as resection or intestinal bypassing should be assessed [19]. Less aggressive surgical procedures such as the insertion of a gastrostomy tube can provide considerable relief in patients with proximal bowel obstructions [20]. In cases where the obstruction is complete and irreversible, the creation of an ostomy (ileostomy, cecostomy or colostomy) may also provide relief [21]. In some cases of large bowel obstruction, colonic endoluminal stenting devices [22, 23] can be considered in the setting of a short fecal obstruction.

Table 5. Laxative medications

<table>
<thead>
<tr>
<th>Category</th>
<th>Mechanisms</th>
<th>Examples</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulking</td>
<td>Hydrophilic increase in fecal bulk</td>
<td>Dietary fiber bran, psyllium</td>
<td>Avoid in bedidden, dehydrated or impacted patients. Not recommended for opioids</td>
</tr>
<tr>
<td>Osmotic wetting agents</td>
<td>Draw water into the intestine, promote peristalsis by mechanical distention</td>
<td>Lactulose</td>
<td>Monitor glucose in diabetics using lactulose. May cause flatulence or colic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Magnesium citrate</td>
<td>In renal failure may cause hypermagnesaemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epsom salts</td>
<td>May cause hyperphosphataemia, hypocalcemia, and fluid and sodium overload</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sorbitol</td>
<td></td>
</tr>
<tr>
<td>Contact irritants/ stimulants</td>
<td>Alter water and electrolyte secretion.</td>
<td>Bisadocyl</td>
<td>Most helpful in patients with loss of rectal reflex or weak abdominal or perineal musculature</td>
</tr>
<tr>
<td></td>
<td>Stimulate colonic motility</td>
<td>Senna</td>
<td>May cause cramping</td>
</tr>
<tr>
<td>Stool softener surfactants emollients</td>
<td>Promote mixing of fat and water, allowing fat to penetrate stool. Increased absorption of other laxatives</td>
<td>Docusate sodium</td>
<td></td>
</tr>
<tr>
<td>Lubricants</td>
<td>Prevent absorption of water</td>
<td>Glycerin suppositories</td>
<td>Avoid mineral oil in the elderly people because of risk of aspiration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>paraffin oil</td>
<td></td>
</tr>
<tr>
<td>Enemas/ suppositories</td>
<td>Local agents that distend colon resulting in reflex evacuation</td>
<td>2–60 min</td>
<td>Avoid soapy enemas because of extreme irritating effect</td>
</tr>
</tbody>
</table>

Principles of medical management

Hydration
Patients should be well hydrated, taking in to account losses that may be incurred by vomiting in the setting of a proximal obstruction [24].

Nasogastric tubes
These may be used temporarily until the obstruction resolves, but where the obstruction is irreversible, other options such as the insertion of a gastrostomy tube should be considered [24].

Antiemetic agents
These agents, which have prokinetic properties, are relatively contraindicated in the presence of a complete obstruction, and alternative agents such as an antihistamine or haloperidol may be required [24].

Corticosteroids
Several controlled studies and a meta-analysis suggest that corticosteroids (e.g. dexamethasone at a starting dose of 20–40 mg/day) may be useful for malignant bowel obstruction [25]. In many cases a partial obstruction may be relieved. The mechanism of this effect is not well established. It is hypothesized that there is a reduction in intramural edema. The optimal dose and duration of treatment has not been clarified.

Gastrograffin
The hyperosmolar oral contrast medium, gastrograffin, may also reduce mural edema and may help resolve episodes of partial small bowel obstruction [26].
**Octreotide**

In patients with severe vomiting from a proximal bowel obstruction, octreotide, a somatostatin analog (100–500 μg subcutaneously or intravenously three times a day, or by continual infusion), may reduce proximal gastrointestinal secretions and vomiting [27]. Octreotide also stimulates myoelectric activity within the gut, leading to faster esophageal contractions and greater motility within the rectosigmoid. An indirect analgesic effect due to reduced distension of the bowel and colicky pain can also be achieved, leading to reduction of concurrent opioid therapy.

**Opioids**

In the setting of severe pain, opioids should be administered despite there potential for dysmotility and constipation [24].

**Antispasmodic agents**

If the obstruction causes severe colic, hyoscine butylbromide may be considered [28].

**Diarrhea**

Diarrhea is much less frequent than constipation; diarrhea is reported in 7 to 10% of cancer patients in hospice care. Common causes are listed in Table 6.

**General management**

Patients must be rehydrated. In cases of large volume diarrhea, there is the potential for very rapid dehydration, with the risk of pre-renal impairment or even, in extreme cases, shock. Patients may suffer electrolyte imbalance, particularly from hypokalemia. In general, milk products should be avoided if an infectious cause is suspected, because a transient lactase deficiency may sometimes occur.

**Table 6. Causes of diarrhea among cancer patients**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Laxatives</th>
<th>Antibiotics</th>
<th>Antacids</th>
<th>5-fluorouracil</th>
<th>Irinotecan</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>Pelvic radiotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intestinal obstruction</td>
<td>Fecal impaction with overflow</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Concurrent disease</td>
<td>Inflammatory bowel disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malabsorption</td>
<td>Pancreatic cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Biliary obstruction</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Fistula</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Short bowel</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Islet cell tumors</td>
<td>Carcinoid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>VIPoma</td>
</tr>
</tbody>
</table>

VIPoma, vasoactive intestinal peptide-producing tumor.

**Medical management**

**Opioids**

Loperamide is the opioid of choice because it has local activity in the gut and is absorbed only minimally (this accounts for the lack of systemic effects). Other opioids, such as morphine or codeine, can be used. This approach has the additional benefit of increasing tone in the anal sphincter.

**Octreotide**

Octreotide is recommended for patients with refractory chemotherapy-induced diarrhea and those with diarrhea caused by secretory islet cell tumors. In this setting, it is useful to start with 1000–1500 μg/day, which is tapered down in the setting of response.

**Dysphagia**

Dysphagia is defined as the difficulty in transferring liquids or solids from the mouth to the stomach.

**Common causes**

**Obstructive**

Cancer-related dysphagia is most often caused by mechanical obstruction. Tumors of the mouth and upper pharynx cause early symptoms, while those of the lower pharynx and esophagus are often silent at first. Food will collect proximally and may spill over into an unprotected airway. Esophageal strictures may occur develop after surgery, radiotherapy or because of gastroesophageal reflux disease.

**Oropharyngeal**

Inability to raise the posterior tongue because of tumor infiltration may allow food to trickle into the pharynx and into an unprotected airway.

**Neurogenic**

Fibrosis following surgery or radiotherapy can damage neural structures and can seriously disrupt the swallowing phases. Cranial nerve damage is often associated with dysesthesias and pain, particularly in the territories of cranial nerves 5 and 9. Indeed, vagal and sympathetic invasion combined with local fibrosis and tumor infiltration can cause severe functional dysphagia that is indistinguishable from gross mechanical obstruction.

**Inflammatory**

Mucosal inflammation due to infection, radiotherapy or chemotherapy may cause painful dysphagia (odynophagia). *Candida* may affect the mouth, pharynx and esophagus. Oral *Candida* is found in only 50% of patients with esophageal candidiasis.
**Clinical evaluation**

The patient’s description can provide useful information: obstructing lesions generally produce dysphagia for solids initially, whereas neuromuscular disorders may cause dysphagia for both solids and liquids, simultaneously. Localization by the patient of an obstruction is often very accurate.

Videofluoroscopy under the direction of a swallowing therapist has become the gold standard of assessing dysphagia, but weakness, immobility and cognitive impairment can prevent its use. For patients with esophageal obstruction, barium or gastrograffin swallow is useful.

**General management principles**

*Hydration*

Evaluate hydration status and where necessary rehydrate. If hydration is appropriate but there is complete obstruction, non-oral hydration will be required. Parenteral nutrition is rarely appropriate in the last weeks or days of a person’s life.

Treat readily amenable causes such as mucositis or esophageal candidiasis.

If the patient has a neurogenic cause for difficulty in swallowing, consider the role of specific rehabilitative therapy. This is often done by specially trained speech therapists, occupational therapists and, sometimes, by physiotherapists.

Evaluate the role for local treatments (see below). If these are not possible or if the patient’s performance status precludes intervention, consider the role of a feeding gastrostomy or jejunostomy.

*Local approaches for esophageal tumors*

*Dilatation*

Benefit from endoscopic dilatation generally lasts less than 2 weeks [29, 30]. Endoscopic dilatation is therefore used mostly as a short-term measure before other measures.

*Brachytherapy*

Short courses of brachytherapy for esophageal cancer has a moderate rate of success that is often well maintained for more than 6 months [31, 32].

*Endoscopic stenting*

This is usually performed with self-expanding metal stents [33, 34]. Such stents can provide effective palliation with median survival times of 4 months (range 1–24) when combined with laser therapy to remove any recurrent, overgrowing tumor [35, 36]. Covered expandable prostheses are better if palliating a fistula or perforation [37].

*Endoscopic laser*

Most data on palliation for esophageal carcinoma have been generated using neodymium:yttrium-aluminum-garnet (Nd:YAG). This approach restores swallowing in 85% of patients. Risks and adverse effects are relatively uncommon:

- risk of perforation 0 to 4%, tracheo-esophageal fistula 0 to 9%, and 30 day mortality 1 to 3%. Compared with stent placement, Nd:YAG tumor ablation appears to offer better palliation of dysphagia, with lower morbidity for tumors <5 cm in length [38]. When the tumor is >5 cm in axial length, however, self-expanding metal stents appear to offer superior palliation to Nd:YAG laser tumor ablation, and should be attempted first. The dysphagia-free interval post-Nd:YAG laser tumor ablation averages only 2–4 months due to tumor regrowth.

*Photodynamic therapy*

Photodynamic therapy (PDT) is a non-thermal ablative technique that involves administration of a photosensitizer followed by light application of the appropriate wavelength to initiate a photo-oxidative reaction that results in tumor cell death and necrosis. The best experience has been reported with the use of the photosensitizer, Photofrin II, which is administered 40–50h before exposure to red light from an argon-pumped dye laser. PDT-induced cytotoxicity occurs over hours to days. Two to 3 days later the patient is re-endoscoped, to debride necrotic tumor and to retreat if viable tumor persists. Palliation of dysphagia is usually evident 5–7 days post-PDT treatment. Patients must be educated about the precautions necessary because of the 6-week period of photosensitivity associated with Photofrin II. Comparative studies suggest that PDT is safer and more effective than laser therapy [39].

*Painful swallowing*

Mucosal pain in the mouth can be eased by topical analgesics such as choline salicylate gel or benzydamine mouthwash, which are topical non-steroidal anti-inflammatory drugs with a mild local anesthetic action [40]. In a Cochrane analysis based on the findings of 15 trials only allopurinol, vitamin E and opioids were found to be effective [41]. A recent systematic analysis was unable to demonstrate clear evidence of benefit from antimicrobial therapies [42].

*Hiccup*

Hiccup is a pathological respiratory reflex characterized by spasm of one or both sides of the diaphragm, resulting in sudden inspiration and closure of the glottis. The incidence of troublesome hiccup in advanced cancer is not known.

*Causes*

Among cancer patients, common causes include diaphragmatic irritation, uremia or medications (particularly corticosteroids) [43]. Occasionally hiccuping may be associated with hypotremia, hypocalcemia or myocardial infarction.

*Management principles*

Mild hiccups may respond to simple physical treatments such as stimulation of the pharynx with a plastic or rubber suction catheter, nebulized saline every 4 h or palatal massage using
a cotton wool ball. Traditional remedies, such as the rapid ingestion of two heaped teaspoons of granulated sugar, the rapid ingestion of two glasses of liqueur, swallowing dry bread, swallowing crushed ice or drinking from the wrong side of a cup, all involve pharyngeal stimulation. Breath holding and rebreathing into a bag generate hypercapnia, which has a central depressant effect that blocks the central component of the hiccup reflex.

Anecdotally, the most effective symptomatic therapy is baclofen, which is effective in doses as small as 5–10 mg twice a day, although occasionally 20 mg three times a day have been necessary [44, 45]. More limited experience has been reported with gabapentin, nifedipine or haloperidol [44, 46]. Although widely used in the past, chlorpromazine is not recommended because of its adverse effects [47]. In the event of hiccups that continue to be troublesome, intravenous midazolam can be used.

### Cholestatic pruritus

Pruritus is the major symptom of obstructive jaundice. Pruritus may occur with any type of liver disease, but is primarily associated with acute or chronic cholestasis. It has been estimated to occur in 20 to 50% of patients with jaundice. The intensity of the pruritus varies from mild to severe. It can be persistent or intermittent, and it may be generalized or localized to specific parts of the body, commonly the soles of the feet and palms of the hands. For patients with symptomatic biliary obstruction, when possible, biliary drainage should be re-established with stenting, entero-biliary anastomosis or percutaneous drainage.

The management of pruritus in this setting is often difficult, and it should involve specific anti-pruritic therapies along with general supportive measures.

### Symptomatic care

**Anion exchange resins**

Anion exchange resins, which are given by mouth, bind bile acids and other anionic compounds in the intestine, resulting in increased fecal excretion of bound substances. This decreases the enterohepatic circulation of bile acids. The most widely administered treatment for the pruritus of cholestasis has been the basic anion exchange resin cholestyramine, but another resin, colestipol, is also available [48, 49]. The maximum recommended dose of cholestyramine is 16 g/24 h. The resin should be taken at least 2 h apart from other medications to ensure adequate absorption of the latter.

**Antihistamines**

Despite their common application, antihistamines are rarely effective in this setting.

**Phenobarbital**

Phenobarbital may relieve pruritus in individual patients, but its utility has not been supported in controlled trials [50]. The barbiturate phenobarbital has sedative effects as well as effects on the liver. This drug non-specifically increases the activity of the hepatic microsomal enzyme system by enzyme induction, and it is hypothesized that it may act by enhancing the excretion of pruritogens.

**Rifampicin**

Rifampicin is another microsomal enzyme inducer. There are conflicting data regarding the efficacy of rifampicin. When effective, the onset of effect is relatively rapid. The usual dose is 300–600 mg/day in divided oral doses [51]. In a double-blind, crossover, randomized, short-term study that included nine patients with primary biliary cirrhosis, rifampicin therapy at doses of 150 mg orally twice a day or 150 mg three times a day in patients with serum bilirubin <3 or >3 mg/dl, respectively, was reported to be associated with amelioration of the pruritus of cholestasis as assessed by a visual analog scale of the perception of pruritus [52].

**Opioid antagonists**

The observation that intravenous naloxone can reduce cholestatic pruritus [53, 54] prompted trials of therapy with orally administered antagonists nalmefene and naltrexone. In an open-label study of nalmefene, 2 mg orally twice was associated with a significant subjective amelioration of pruritus, as measured by a visual analog scale of pruritus, and a significant decrease in scratching activity [55]. Naltrexone at doses of 50 mg per day has been studied in a placebo-controlled study of patients with the pruritus of cholestasis without apparent toxicity and with subjective relief of their pruritus as assessed subjectively [56]. In a small study, some patients achieved relief with buprenorphine [57].

**5-HT3 antagonists**

Very limited data from a small placebo-controlled study support a trial of the 5-HT3 antagonist ondansetron in the management of cholestatic pruritus [58].

**Other measures**

In addition to these specific therapies, simple measures have been recommended. Such measures include the use of emollients and mild fragrance-free soaps (e.g. fragrance-free Dove, Basis, Aveeno), less frequent bathing, wearing light clothing and frequent cutting of fingernails.

### References