Chapter 6

Gastroenterology

In this chapter

Background

The main function of the gastrointestinal (GI) tract is to break food down into a suitable energy source to allow normal physiological function of cells. Needless to say, the process is complex and involves many different organs. Consequently, there are many conditions that affect the GI tract, some of which are acute and self-limiting and respond well to OTC medication and others that are serious and require referral.

General overview of the anatomy of the GI tract

It is vital that pharmacists have a sound understanding of GI tract anatomy. Many conditions will present with similar symptoms and from similar locations, for example abdominal pain, and the pharmacist will need a basic knowledge of GI tract anatomy – and in particular of where each organ of the GI tract is located – to facilitate a correct differential diagnosis.

Oral cavity

The oral cavity comprises the cheeks, hard and soft palates and tongue.

Stomach

The stomach is roughly 'J' shaped and receives food and fluid from the oesophagus. It empties into the duodenum. It is located slightly left of midline and anterior (below) to the rib cage. The lesser curvature of the stomach sits adjacent to the liver.

Liver

The liver is located below the diaphragm and mostly right of midline in the upper right quadrant of the abdomen. The liver performs many functions, including carbohydrate, lipid and protein metabolism and the processing of many medicines.

Gall bladder

The gall bladder is a pear-shaped sac that lies deep to the liver and hangs from the lower front margin of the liver. Its function is to store and concentrate bile made by the liver.

Pancreas

The pancreas lies behind the stomach. It is essential for producing digestive enzymes transported to the duodenum via the pancreatic duct and secretion of hormones such as insulin.

History taking and physical exam

A thorough patient history is essential as physical examination of the GI tract in a community pharmacy is limited to inspection of the mouth. This should allow confirmation of the diagnoses for conditions such as mouth ulcers and oral thrush. A description of how to examine the oral cavity appears in the following section.

Conditions affecting the oral cavity

Background

The process of digestion starts in the oral cavity. The tongue and cheeks position large pieces of food so that the teeth can tear and crush food into smaller particles. Saliva moistens, lubricates and begins the process of digesting carbohydrates (by secreting amylase enzymes) prior to swallowing,

The physical exam

The oral cavity can easily be observed in the pharmacy provided the mouth can be viewed with a good light source, preferably a pen torch (Fig. 6.1). The patient will usually present with some form of oral lesion and/or pain in a particular part of the mouth. The pharmacist should examine this area carefully, but the rest of the oral cavity should also be inspected. Checks for periodontal disease (bleeding gums) and other sites of mouth soreness should be performed. The floor of the mouth and underside of the tongue can be viewed by asking the patient to curl the tongue towards the roof of the mouth; the buccal mucosa is best observed when the patient half opens the mouth.

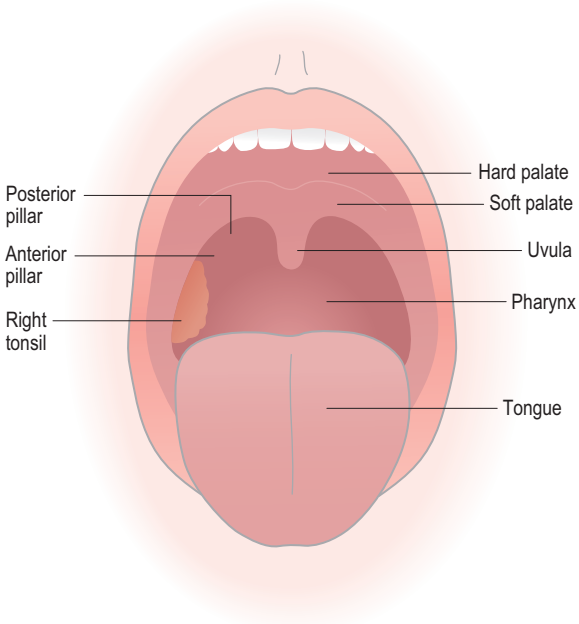

Fig. 6.1 The oral cavity

Mouth ulcers

Background

Aphthous ulcers, more commonly known as mouth ulcers, is a collective term used to describe various different clinical presentations of superficial painful oral lesions that occur in recurrent bouts at intervals between a few days to a few months. The majority of patients (80%) who present in a community pharmacy will have minor aphthous ulcers (MAU). It is the community pharmacists' role to exclude more serious pathology, for example, systemic causes and carcinoma.

Prevalence and epidemiology

The prevalence and epidemiology of MAU is poorly understood. They occur in all ages but it has been reported that they are more common in patients aged between 20 and 40, and up to 66% of young adults give a history consistent with MAU. Lifetime prevalence is estimated to affect one in five of the general population.

Aetiology

The cause of MAU is unknown. A number of theories have been put forward to explain why people get MAU, including stress, trauma, food sensitivities, nutritional deficiencies (iron, zinc and vitamin B_{12}) and infection, but none have so far been proven.

Arriving at a differential diagnosis

There are three main clinical presentations of ulcers: minor, major or herpetiform. Although it is likely the patient will be suffering from MAU it is essential that these and other causes are recognised and referred to the GP for further evaluation. A number of ulcer-specific questions should always be asked of the patient to aid in diagnosis (Table 6.1). After questioning the patient, the oral cavity should be inspected to confirm the diagnosis.

Clinical features of minor aphthous ulcers

The ulcers of MAU are roundish, grey-white in colour and painful. They are small – usually less than 1 cm in diameter – and shallow with a raised red rim. Pain is the key presenting symptom and can make eating and drinking difficult, although pain subsides after 3 or 4 days. They rarely occur on the gingival mucosa and occur

Table 6.1
Specific questions to ask the patient: Mouth ulcers

Question	Relevance
Number of ulcers	• MAU occur singly or in small crops. A single large ulcerated area is indicative of more serious pathology • Patients with numerous ulcers are more likely to be suffering from other forms of ulceration such as major or herpetiform ulcers rather than MAU
Location of ulcers	• Ulcers on the side of the cheeks, tongue and inside of the lips are likely to be MAU • Ulcers located towards the back of the mouth are more consistent with major or herpetiform ulcers
Size and shape	• Irregular-shaped ulcers tend to be caused by trauma. If trauma is not the cause then referral is necessary to exclude sinister pathology • If ulcers are large or very small they are unlikely to be caused by MAU
Painless ulcers	• Any patient presenting with a painless ulcer in the oral cavity must be referred. This can indicate sinister pathology such as leukoplakia or carcinoma
Age	• MAU in young children (< 10 years old) is not common and other causes such as primary infection with herpes simplex should be considered. If MAU is suspected, and it is the first time the patient has had ulcers, then referral should be considered to confirm the diagnosis • If ulcers appear for the first time after adolescence then the diagnostic probability is increased for them to be caused by things other than MAU

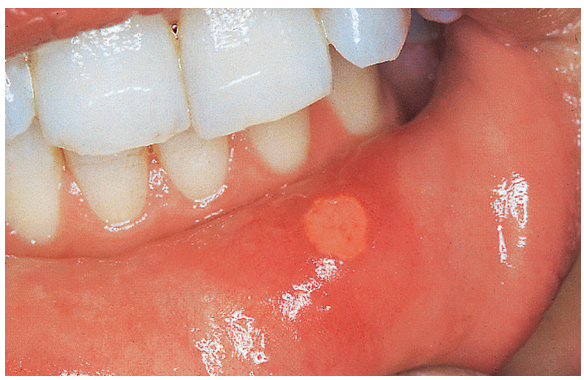

Fig. 6.2 Minor aphthous ulcer. Reproduced from *Essentials of Oral Pathology and Oral Medicine* by R Cawson et al, 2002, Churchill Livingstone, with permission

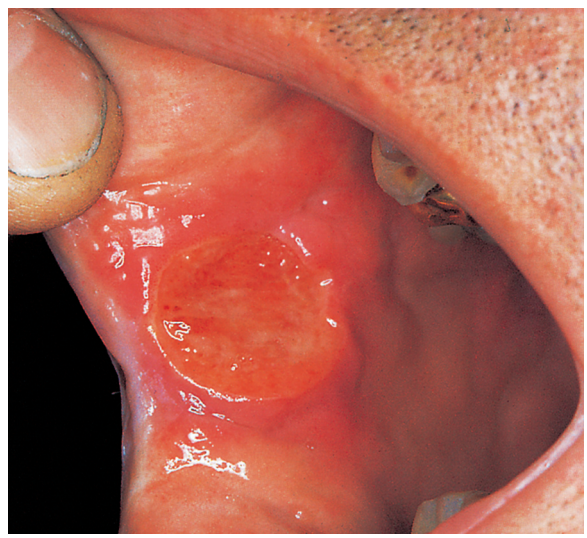

Fig. 6.3 Major aphthous ulcer. Reproduced from *Essentials of Oral Pathology and Oral Medicine* by R Cawson et al, 2002, Churchill Livingstone, with permission

singly or in small crops of up to five ulcers. It normally takes 7 to 14 days for the ulcers to heal but recurrence typically occurs after an interval of 1 to 4 months (Fig. 6.2).

Conditions to eliminate

Major aphthous ulcers

Characterised by large (greater than 1 cm in diameter) numerous ulcers, in crops of 10 or more. The ulcers often coalesce to form one large ulcer. The ulcers heal slowly and can persist for many weeks (Fig. 6.3).

Herpetiform ulcers

Herpetiform ulcers are pinpoint and occur in large crops of up to 100 at a time. They usually heal within a month and often occur in the posterior part of the mouth, an unusual location for MAU (Fig. 6.4). Both herpetiform and major aphthous ulcers are approximately ten times less common than MAU.

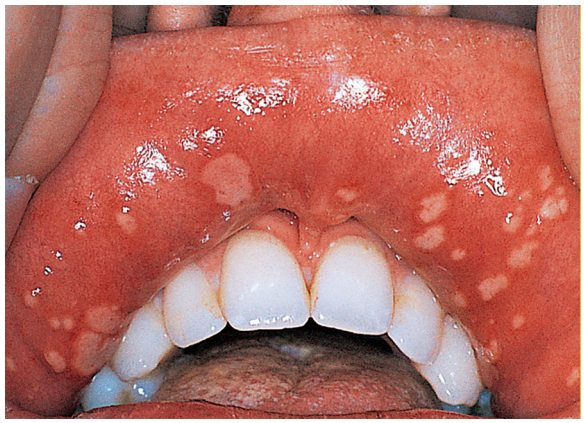

Fig. 6.4 Herpetiform ulcer. Reproduced from *Essentials of Oral Pathology and Oral Medicine* by R Cawson et al, 2002, Churchill Livingstone, with permission

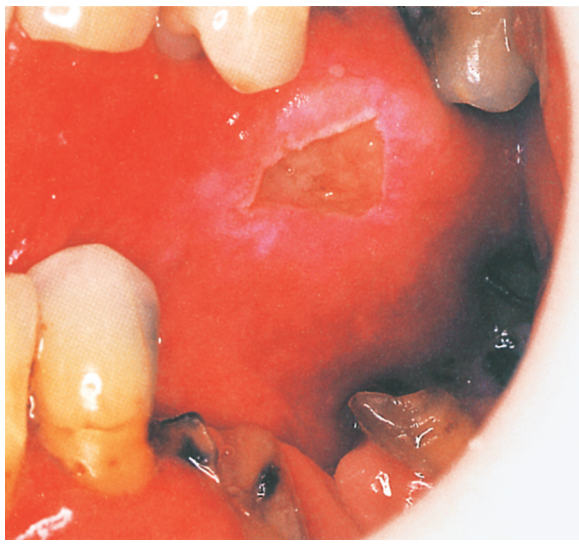

Fig. 6.5 Ulcer caused by trauma. Reproduced from *Textbook of General and Oral Medicine* by D Wray et al, 1999, Churchill Livingstone, with permission

Trauma

Trauma to the oral mucosa will result in damage and ulceration. Trauma may be mechanical (e.g. tongue biting) or thermal resulting in ulcers with an irregular border. Patients should be able to recall the traumatic event and have no history of ulceration or signs of systemic infection (Fig. 6.5).

Oral thrush

Oral thrush usually presents as creamy-white soft elevated patches. It is covered in more detail in the next section and the reader is referred to pages 129–131 for differential diagnosis of thrush from other oral lesions.

Herpes simplex

Herpes simplex virus is a common cause of oral ulceration in children. Primary infection results in ulceration of any part of the oral mucosa, especially the gums, tongue and cheeks. The ulcers tend to be small and discrete and many in number. Prior to the eruption of ulcers the person might show signs of systemic infection such as fever and pharyngitis.

Medicine-induced ulcers

A number of case reports have been received of medication causing ulcers. These include: cytotoxic agents, nicorandil, alendronate, NSAIDs and beta-blockers.

Squamous cell carcinoma

Squamous cell carcinoma is the most common oral malignant lesion in the UK, with approximately 2000 people diagnosed each year and 800 deaths. It is twice as common in men than women, and 90% of people are aged over 40 years when diagnosed; the average age at diagnosis is 64 for men and 61 for women. Smokers are at increased risk and account for 75% of cases; therefore, patients should always be asked about their smoking history.

The majority of cancers are noted on the side of the tongue, mouth and lower lip. Initial presentation ranges from painless spots, lumps or ulcers in the mouth or lip area that fail to resolve. Over time these become painful, change colour or bleed. The painless nature of early symptoms leads people to seek help only when other symptoms become apparent. Symptoms therefore can be present for a number of weeks before the patient presents to a healthcare practitioner. Urgent referral is needed as survival rates increase dramatically if the disease is diagnosed in its early stages.

Erythema multiforme

Infection or drug therapy can cause erythema multiforme, although in about 50% of cases no cause can be found. Symptoms are sudden in onset causing widespread ulceration of the oral cavity. In addition, the patient can have annular and symmetric erythematous skin lesions located towards the extremities. Conjunctivitis and eye pain are also common.

Behcet's syndrome

Most patients will suffer from recurrent, painful major aphthous ulcers that are slow to heal. Lesions are also observed in the genital region and eye involvement (iridocyclitis) is common.

Figure 6.6 will aid the differentiation between serious and non-serious conditions that cause mouth ulcers.

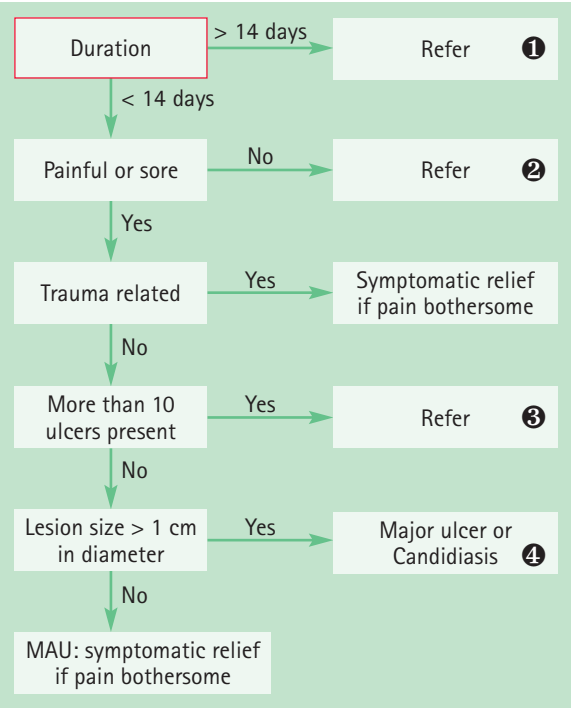

Fig. 6.6 Primer for differential diagnosis of mouth ulcers

❶ Duration
MAU normally resolve in 7 to 14 days. Ulcers that fail to heal within this time need referral to exclude other causes.

❷ Painless ulcers
These can indicate sinister pathology, especially if the patient is over 50 years old. In addition, it is likely that the ulcer will have been present for some time before the patient presented to the pharmacy.

❸ Numerous ulcers
Crops of 5 to 10 or more ulcers are rare in MAU. Referral is necessary to determine the cause.

❹ Major ulcer or candidiasis
See Fig. 6.9 for primer for differential diagnosis of oral thrush.

TRIGGER POINTS indicative of referral: Mouth ulcers

- Children under 10
- Duration longer than 14 days
- Painless ulcer
- Signs of systemic illness, e.g. fever
- Ulcers greater than 1 cm in diameter
- Ulcers in crops of five to ten, or more

Evidence base for over-the-counter medication

A wide range of products are marketed for the temporary relief and treatment of mouth ulcers. These products contain corticosteroids, local anaesthetics, antibacterials, astringents and antiseptics.

Corticosteroids

Very few random controlled trials have been conducted using topical corticosteroids. Those conducted involved small patient numbers or products that are not commercially available OTC. A review by Porter and Scully in *Clinical Evidence* (http://clinicalevidence.bmj.com/ceweb/index.jsp) concluded that corticosteroids did heal ulcers more quickly than control preparations. However, this review included products not available OTC in the UK. Specific trial data for commercially available products in the UK are therefore discussed.

Triamcinolone acetonide 0.1% in Orabase

Triamcinolone acetonide was deregulated from POM to P status in 1994. It has been suggested as a useful preparation to treat MAU by a number of authors, although there is a lack of clinical evidence from trial data. A study by Browne et al (1968) failed to demonstrate statistically significant improvement in the time it took to heal ulcers, although subjective improvements were noted by patients using triamcinolone in Orabase and not by those using Orabase alone. The improvements were minor and the authors suggest that triamcinolone in Orabase should not be used for routine use and reserved for severe episodes. A further trial, which evaluated triamcinolone, Orabase, betametasone 0.1 mg tablets and carbenoxolone gel failed to demonstrate statistical improvement for any of the treatments.

Hydrocortisone sodium succinate (Corlan) pellets

Only one trial conducted by Truelove et al (1958) could be found that investigated the efficacy of hydrocortisone sodium succinate pellets. At the request of the authors, a specific tablet formulation of hydrocortisone was made, which could be placed on the surface of the ulcer. The request was made because attempts using hydrocortisone ointment were largely unsuccessful as oral fluids washed the ointment away. The authors recruited 52 patients suffering from various forms of oral ulceration; 23 of the patients were suffering from minor aphthous ulceration. The authors stated that 22 of the 23 patients obtained rapid relief of pain and the healing rate of the ulcers was accelerated. However, the study lacked randomisation, a placebo or blinding. Owing to the limited data and poor trial design it is difficult to say whether hydrocortisone succinate pellets are effective, better than placebo or indeed have any effect at all.

Antibacterial agents (e.g. chlorhexidine)

A number of random controlled trials have investigated antibacterial mouthwashes containing chlorhexidine

Table 6.2
Practical prescribing: Summary of medicines for ulcers

Name of medicine	Use in children	Likely side effects	Drug interactions of note	Patients in whom care should be exercised	Pregnancy and breast-feeding
Adcortyl in Orabase	Yes but manufacturers do not state a lower age limit	None	None	None	Inadequate evidence, best to avoid use
Corlan	>12 years	None			
Choline salicylate	>10 years*				OK
Lidocaine		Can cause sensitisation reactions			
Benzocaine					
Carmellose	Yes	None			
Chlorhexidine	Yes but manufacturers do not state a lower age limit	None			

*Age limit is arbitrarily set by author. Marketed products do have licences for use in younger people

gluconate. Data from some, but not all studies, have found that they reduced the pain and severity of each episode of ulceration.

Products containing anaesthetic or analgesics

There are very little trial data to support the pain-relieving effect of anaesthetics or analgesics in MAU, apart from choline salicylate. However, these preparations are clinically effective in other painful oral conditions. It is therefore not unreasonable to expect some relief of symptoms to be shown when using these products to treat MAU.

Choline salicylate

Choline salicylate has been shown to exert an analgesic effect in a number of small studies. However, only one study by Reedy (1970) involving 27 patients evaluated choline salicylate in the treatment of oral aphthous ulceration. No significant differences were found between choline salicylate and placebo in ulcer resolution but choline salicylate was found to be significantly superior to placebo in relieving pain.

Protectants

Orabase is a paste of gelatin, pectin and carmellose sodium, which sticks when it comes in contact with wet mucosal surfces. There is a paucity of data to support its efficacy. However, it has no known side effects, and can be used in any patient population. It should be noted that Orabase contains no pain-relieving agents, and only protects the ulcer from further abrasion. Therefore, it is often used in combination with anaesthetics or analgesics.

HINTS AND TIPS BOX 6.1: ULCERS

Application of Adcortyl	Apply after food, as food is likely to rub off the paste

Practical prescribing and product selection

Prescribing information relating to the medicines used for ulcers reviewed in the section 'Evidence base for over-the-counter medication' is discussed and summarised in Table 6.2; useful tips relating to patients presenting with ulcers are given in Hints and Tips Box 6.1.

Triamcinolone acetonide 0.1% in Orabase (Adcortyl in Orabase 0.1%)

Adcortyl should be applied between two and four times a day for up to 5 days. All patient groups can use the product and it is well tolerated with no side effects reported. Because it is locally applied there are no drug interactions.

Hydrocortisone sodium succinate pellets (Corlan pellets)

Each pellet contains 2.5 mg hydrocortisone in the form of the ester hydrocortisone sodium succinate. The dose for adults and children over 12 years is one pellet to be dissolved in close proximity to the ulcers four times a day for up to 5 days. It does not interact with any medicines, can be taken by all patient groups and has no side effects.

(Note: For both products, triamcinolone and hydrocortisone sodium succinate, there is inadequate evidence of safety in pregnancy and breast-feeding and therefore manufacturers advise avoidance.)

Choline salicylate (Bonjela)

Choline salicylate is licensed from 4 months upwards for the treatment of soreness in the mouth (e.g. teething pain); however, it would be good practice to refer children under 10 years old presenting with MAU for the first time. Adults and children over 10 years old should apply the gel, using a clean finger, over the ulcer every 3 hours or when needed. It is a very safe medicine and can be given to all patient groups. It is not known to interact with any medicines or cause any side effects.

Local anaesthetics (lidocaine, e.g. the Anbesol range, Calgel, Medijel and benzocaine, e.g. Rinstead Adult Gel)

All local anaesthetics have a short duration of action; frequent dosing is therefore required to maintain the anaesthetic effect. They are thus best used on a when-needed basis although, depending on the concentration of anaesthetic included in products, the upper limit on the number of applications allowed does vary. In most instances the products should not be used more than eight times in a day. They appear to be free from any drug interactions, have minimal side effects and can be given to most patients. A small percentage of patients might experience a hypersensitivity reaction with lidocaine or benzocaine; this appears to be more common with benzocaine.

Antibacterial agents (e.g. chlorhexidine)

Chlorhexidine (Corsodyl) mouthwash is indicated as an aid in the treatment and prevention of gingivitis and in the maintenance of oral hygiene, which includes the management of aphthous ulceration. Ten millilitres of the mouthwash should be rinsed around the mouth for about 1 minute twice a day. It can be used by all patient groups, including during pregnancy and breast-feeding. Side effects associated with its use include reversible tongue and tooth discolouration, burning of the tongue and taste disturbance.

Carmellose sodium (Orabase Protective Paste)

Orabase can be applied as frequently as required. It is important that it is dabbed on, and not rubbed on, for it to stick correctly. Also, patients should be discouraged from putting too much on as the excess can peel off leaving the lesion exposed. There are no apparent interactions and Orabase can be used in all patient groups.

Further reading

Browne RM, Fox EC, Anderson RJ. Topical triamcinolone acetonide in recurrent aphthous stomatitis. A clinical trial. Lancet 1968;1:565–7.

Davis G. CPPE distance learning. Oral health, vol 2. Recognition and treatment of orofacial problems. London: Outset Publishing Ltd, 1996.

MacPhee IT, Sircus W, Farmer ED, et al. Use of steroids in treatment of aphthous ulceration. Br Med J 1968;2(598):147–9.

Reedy BL. A topical salicylate gel in the treatment of oral aphthous ulceration. Practitioner 1970;204:846–50.

Scully C. Aphthous ulceration. N Engl J Med 2006;355: 165–72.

Truelove SC, Morris-Owen RM. Treatment of aphthous ulceration of the mouth. BMJ 1958;1:603–7.

Zakrzewska JM. Fortnightly review: oral cancer. BMJ 1999;318:1051–4.

Web sites

General site on oral health: http://www.nlm.nih.gov/medlineplus/mouthandteeth.html

The Behcet's Syndrome Society: http://www.behcets-society.fsnet.co.uk/looklike.html

The British Dental Health Foundation: http://www.dentalhealth.org.uk/

Oral thrush (candidiasis)

Background

Oropharyngeal candidiasis (oral thrush) is an opportunistic mucosal infection and is unusual in healthy adults. If oral thrush is suspected in this population, community pharmacists should determine if any identifiable risk factors exist or, if not, suspect potential underlying sinister pathology.

Prevalence and epidemiology

The very young (neonates) and the very old are most likely to suffer from oral thrush. It has been reported that 5% of newborn infants and 10% of debilitated elderly patients suffer from oral thrush. Most other cases will be associated with underlying pathology such as diabetes, xerostomia (dry mouth), patients who are immunocompromised or be attributable to identifiable risk factors

such as recent antibiotic therapy, inhaled corticosteroids and ill-fitting dentures.

Aetiology

It is reported that *Candida albicans* is found in the oral cavity of 30 to 60% of healthy people in developed countries (Gonsalves et al 2007). It is transmitted directly between infected people or via objects that can hold the organism. Prevalence in denture wearers is even higher. Changes to the normal environment in the oral cavity will allow *C. albicans* to proliferate.

Arriving at a differential diagnosis

Oral thrush is not difficult to diagnose with the aid of a careful history and an oral examination. It is the role of the pharmacist to eliminate underlying pathology and exclude risk factors. A number of oral thrush specific questions should always be asked of the patient (Table 6.3). After questioning the pharmacist should inspect the oral cavity to confirm the diagnosis.

Clinical features of oral thrush

The classical presentation of oral thrush is of creamy-white soft elevated patches that can be wiped off revealing underlying erythematous mucosa (Fig. 6.7). Pain, soreness, altered taste and a burning tongue can be present. Lesions can occur anywhere in the oral cavity but usually affect the tongue, palate, lips and cheeks. Patients sometimes complain of malaise and loss of appetite. In neonates, spontaneous resolution usually occurs but can take a few weeks.

Table 6.3
Specific questions to ask the patient: Oral thrush

Question	Relevance
Size and shape of lesion	• Typically, patients with oral thrush present with 'patches'. They tend to be irregularly shaped and vary in size from small to large
Associated pain	• White, painless patches, especially in people aged over 50, should be referred to exclude sinister pathology such as leukoplakia
Location of lesions	• Oral thrush often affects the tongue and cheeks, although if precipitated by inhaled steroids the lesions appear on the pharynx

Conditions to eliminate

Leukoplakia

Leuloplakia is a predominantly white lesion of the oral mucosa that cannot be characterised as any other definable lesion and is therefore a diagnosis based on exclusion (Fig. 6.8). It is often associated with smoking and is a precancerous lesion, although epidemiological data suggest that annual transformation rate to squamous cell carcinoma is approximately 1%. Patients present with a symptomless white patch that develops over a period of weeks on the tongue or cheek. The lesion cannot be wiped off, unlike oral thrush. Most cases are

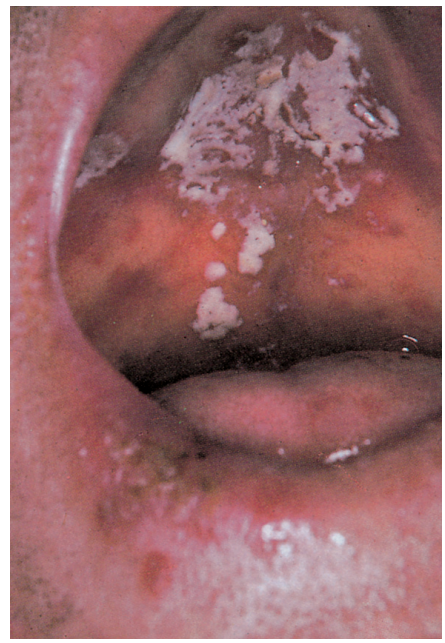

Fig. 6.7 Oral candidiasis. Reproduced from *Illustrated Pocket Guide to Clinical Medicine* by C D Forbes and W F Jackson, 2004, Mosby, with permission

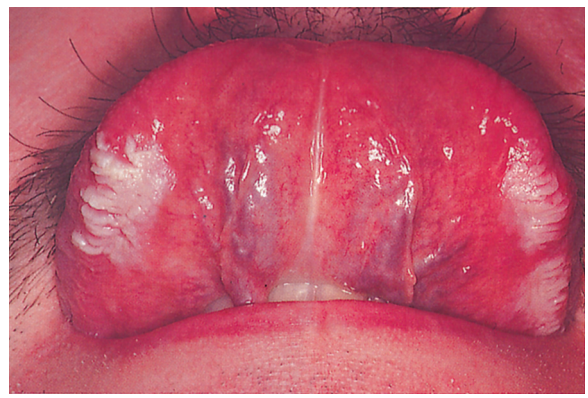

Fig. 6.8 Leukoplakia. Reproduced from *Illustrated Pocket Guide to Clinical Medicine* by C D Forbes and W F Jackson, 2004, Mosby, with permission

seen in people over the age of 40 years and it is more common in men. All suspected cases require referral.

Mouth ulcers and squamous cell carcinoma

Mouth ulcers and squamous cell carcinoma are covered in more detail on pages 124–126 and the reader is referred to this section for differential diagnosis of these from oral thrush.

Lichen planus

Lichen planus is a dermatological condition with lesions similar in appearance to plaque psoriasis. In about 50% of people the oral mucous membranes are affected. The cheeks, gums or tongue develop white, slightly raised painless lesions that look a little like a spider's web. Other symptoms can include soreness of the mouth and a burning sensation. Occasionally, lichen planus of the mouth occurs without any skin rash.

Figure 6.9 will aid the differentiation of thrush from other oral lesions.

TRIGGER POINTS indicative of referral: Oral thrush

- Diabetic
- Duration greater than 3 weeks
- Immunocompromised patients
- Painless lesions

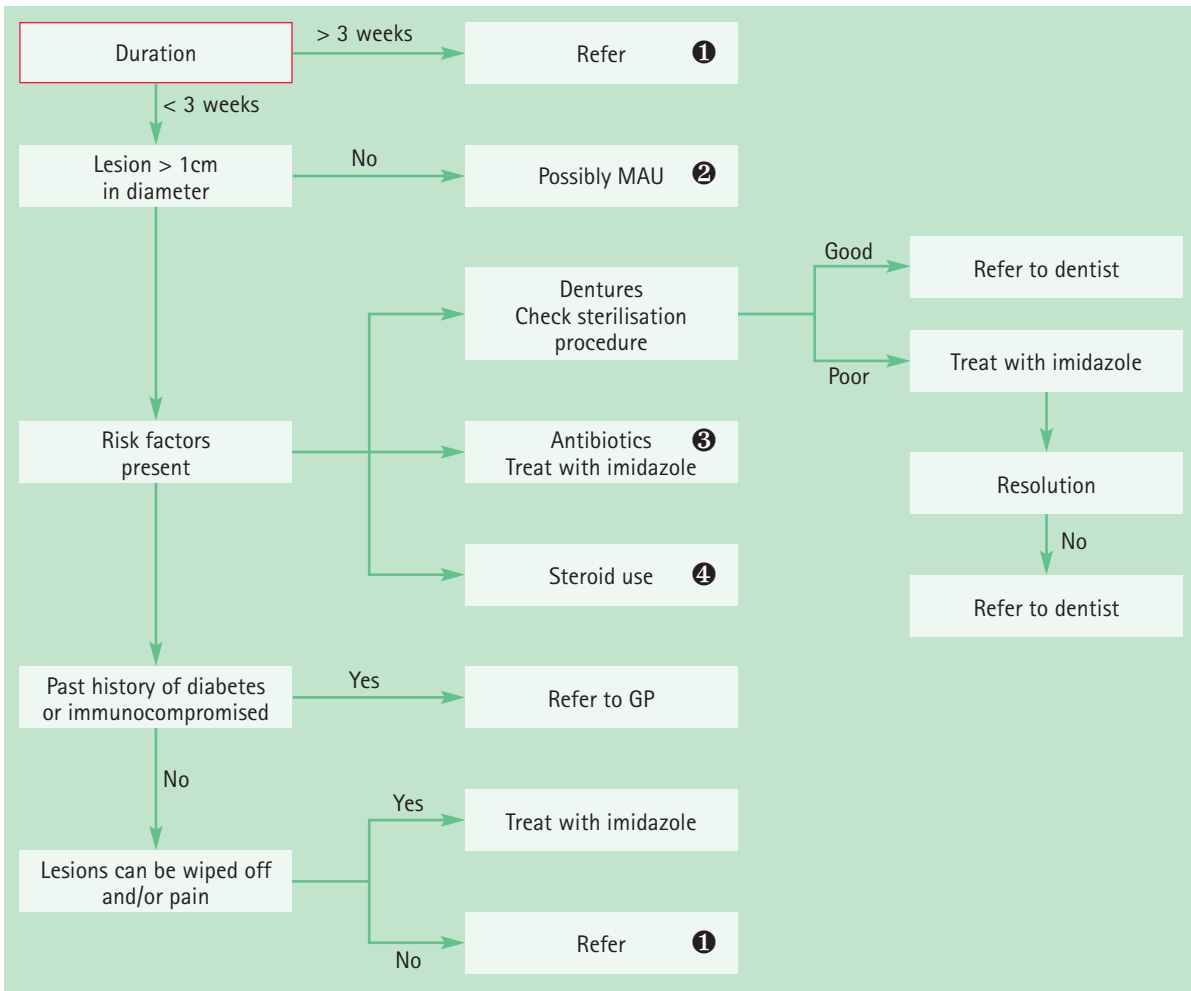

Fig. 6.9 Primer for differential diagnosis of oral thrush

❶ Duration
Any lesion lasting more than 3 weeks must be referred to exclude sinister pathology.

❷ MAU
See Fig. 6.6 for primer for differential diagnosis of mouth ulcers.

❸ Antibiotics
Broad-spectrum antibiotics, e.g. amoxicillin and macrolides, can precipitate oral thrush by altering normal flora of the oral cavity.

❹ Inhaled corticosteroids
High-dose inhaled corticosteroids can cause oral thrush. Patients should be encouraged to use a spacer and wash their mouth out after inhaler use to minimise this problem.

Table 6.4
Practical prescribing: Summary of medicines for oral thrush

Name of medicine	Use in children	Likely side effects	Drug interactions of note	Patients in whom care should be exercised	Pregnancy and breast-feeding
Daktarin	Infants upwards	Nausea and vomiting	Warfarin	None	OK

HINTS AND TIPS BOX 6.2: DAKTARIN

Application of Daktarin	Patients should be advised to hold the gel in the mouth for as long as possible to increase contact time between the medicine and the infection
Duration of treatment	Treatment should be continued for up to 2 days after the symptoms have cleared to prevent relapse and reinfection
Patient acceptability	Gel is flavoured orange to make retention in the mouth more acceptable to patients

Evidence base for over-the-counter medication

Only Daktarin oral gel (miconazole) is available OTC to treat oral thrush. It has proven efficacy and appears to have clinical cure rates between 80 to 90%. In comparative trials, Daktarin appears to have superior cure rates than the POM Nystatin.

Practical prescribing and product selection

Prescribing information relating to Daktarin oral gel reviewed in the section 'Evidence base for over-the-counter medication' is discussed and summarised in Table 6.4; useful tips relating to the application of Daktarin are given in Hints and Tips Box 6.2.

The dose of gel varies dependent on the age of patient and the distribution of the lesions. If lesions are localised then a small amount of gel can be applied directly to the area with a clean finger. For more generalised infections the dose should be given by way of a 5 mL spoon. For adults and children over 6 years, 5 mL of the gel should be applied four times a day and 5 mL used twice a day in children under 6 years. For infants and children under 2 years the dose is 2.5 mL twice a day.

It can occasionally cause nausea and vomiting, but these side effects are rare. The manufacturers state that it can interact with a number of medicines, namely mizolastine, cisapride, triazolam, midazolam, quinidine, pimozide, HMG-CoA reductase inhibitors and anticoagulants. However, there is a lack of published data to determine how clinically significant these interactions are except with warfarin. Co-administration of warfarin with miconazole increases warfarin levels markedly and the patient's international normalised ratio (INR) should be monitored closely. The manufacturers also state that Daktarin should be avoided in pregnancy but published data do not support an association between miconazole and congenital defects.

Further reading

Gonsalves WC, Chi A, Neville BW. Common oral lesions: Part I. Superficial mucosal lesions. Am Fam Phys 2007;75:501–7.

Hoppe JE, Hahn H. Randomized comparison of two nystatin oral gels with miconazole oral gel for treatment of oral thrush in infants. Antimycotics Study Group. Infection 1996;24:136–9.

Hoppe JE. Treatment of oropharyngeal candidiasis in immunocompetent infants: a randomized multicenter study of miconazole gel vs. nystatin suspension. The Antifungals Study Group. Pediatr Infect Dis J 1997;16:288–93.

Parvinen T, Kokko J, Yli-Urpo A. Miconazole lacquer compared with gel in treatment of denture stomatitis. Scand J Dent Res 1994;102:361–6.

Web sites

General information: http://www.netdoctor.co.uk/diseases/facts/oralthrush.htm and http://www.patient.co.uk/

Gingivitis

Background

Gingivitis simply means inflammation of the gums and is usually caused by an excess build-up of plaque on the teeth. The condition is entirely preventable if regular tooth brushing is undertaken. Despite this, dental caries and gum disease still affect almost everyone.

Prevalence and epidemiology

It is estimated that 50% of the UK population are affected by gum disease and that more than 85% of people over 40 years will experience gingival disease. Men more than women tend to suffer from severe gingivitis, which might be due to women practising better oral hygiene.

Aetiology

Following tooth brushing, the teeth soon become coated in a mixture of saliva and gingival fluid, known as pellicle. Oral bacteria and food particles adhere to this coating and begin to proliferate forming plaque; subsequent brushing of the teeth removes this plaque build-up. However, if plaque is allowed to build up for 3 or 4 days, bacteria begin to undergo internal calcification producing calcium phosphate better known as tartar (or calculus). This adheres tightly to the surface of the tooth and retains bacteria in situ. The bacteria release enzymes and toxins that invade the gingival mucosa, causing inflammation of the gingiva (gingivitis). If the plaque is not removed the inflammation travels downwards, involving the periodontal ligament and associated tooth structures (periodontitis). A pocket forms between the tooth and gum and, over a period of years, the root of the tooth and bone are eroded until such time that the tooth becomes loose and lost. This is the main cause of tooth loss in people over 40 years of age.

A number of risk factors are associated with gingivitis and periodontitis; these include diabetes mellitus, cigarette smoking, poor nutritional status and poor oral hygiene.

Arriving at a differential diagnosis

Gingivitis often goes unnoticed because symptoms can be very mild and painless. This often explains why a routine check-up at the dentist reveals more severe gum disease than patients thought they had. A dental history needs to be taken from the patient, in particular details of their tooth brushing routine and technique, as well as the frequency of visits to their dentist. The mouth should be inspected for tell-tale signs of gingival inflammation. A number of gingivitis-specific questions should always be asked of the patient to aid in diagnosis (Table 6.5).

Clinical features of gingivitis

Gingivitis is characterised by swelling and reddening of the gums, which bleed easily with slight trauma, for example when brushing teeth. Plaque might be visible; especially on teeth that are difficult to reach when tooth brushing. Halitosis might also be present.

Table 6.5
Specific questions to ask the patient: Gingivitis

Question	Relevance
Tooth brushing technique	• Overzealous tooth brushing can lead to bleeding gums and gum recession. Make sure the patient is not 'over cleaning' their teeth. An electric toothbrush might be helpful for people who apply too much force when brushing teeth
Bleeding gums	• Gums that bleed without exposure to trauma and is unexplained or unprovoked need referral to exclude underlying pathology

Conditions to eliminate

Periodontitis

If gingivitis is left untreated it will progress into periodontitis. Symptoms are similar to gingivitis but the patient will experience spontaneous bleeding, taste disturbances, halitosis and difficulty while eating. Periodontal pockets might be visible and the patient might complain of loose teeth. Referral to a dentist is needed for evaluation and removal of tartar.

Spontaneous bleeding

A number of conditions can produce spontaneous gum bleeding, for example agranulocytosis and leukaemia. Other symptoms should be present, for example, progressive fatigue, weakness and signs of systemic illness such as fever. Immediate referral to the GP is needed.

Medicine-induced gum bleeding/hypertrophy

Medicines such as warfarin, heparin and NSAIDs might produce gum bleeding. Consultation with the prescriber to suggest alternative medication would be needed. Gum hypertrophy is very common in people taking phenytoin, ciclosporin and nifedipine and patients must be told about these adverse events when they are first prescribed them.

TRIGGER POINTS indicative of referral: Gingivitis

- Foul taste associated with gum bleeding
- Loose teeth
- Signs of systemic illness
- Spontaneous gum bleeding

Evidence base for over-the-counter medication

Put simply, there is no substitute for good oral hygiene. Prevention of plaque build-up is the key to healthy gums and teeth. Once-daily brushing is adequate to maintain oral hygiene at adequate levels. If the patient brushes more regularly than this then this should not be discouraged. Brushing teeth with a fluoride toothpaste, to prevent tooth decay, should preferably take place after eating, and flossing is recommended to access areas that a toothbrush might miss. A recent Cochrane review (Robinson et al 2005) concluded that powered toothbrushes (with rotation oscillation action – where brush heads rotate in one direction and then the other) are more effective than manual brushing at plaque removal.

However, there are a plethora of oral hygiene products marketed for general sale to the public, whether through a pharmacy outlet or a general store. These products should be reserved for established gingivitis or those patients who are unable to use a toothbrush.

Mouthwashes contain chlorhexidine, hexetidine, hydrogen peroxide, sodium perborate and povidone-iodine. Of these, chlorhexidine in concentrations of either 0.1 or 0.2% has been proven the most effective antibacterial in reducing plaque formation and gingivitis (Ernst et al 1998). In clinical trials it has been shown to be consistently more effective than placebo and comparator medicines, and there appears to be no difference in effect between concentrations. It has even been used as a positive control.

Povidone-iodine has antiseptic properties and is beneficial in oral infection but has failed to show a significant effect in decreasing gingivitis and plaque formation except when combined with hydrogen peroxide. Hydrogen peroxide and povidone-iodine might therefore work synergistically because both products alone have failed to demonstrate effectiveness in inhibition of plaque formation.

Practical prescribing and product selection

Prescribing information relating to the medicines used for gingivitis reviewed in the section 'Evidence base for over-the-counter medication' is discussed and summarised in Table 6.6; useful tips relating to products for oral care are given in Hints and Tips Box 6.3.

All mouthwashes, except those containing iodine, appear to be free from any drug interactions, have minimal side effects and can be used by all patient groups. They are rinsed around the mouth for between 30 seconds and 1 minute then spat out.

Chlorhexidine gluconate (e.g. Corsodyl 0.2%, Eludril 0.1%)

The standard dose for adults and children is 10 mL twice a day. Although it is free from side effects, patients should be warned that prolonged use may stain the tongue and teeth brown. This can be reduced or removed by brushing teeth before use. If this fails to remove the staining then it can be removed by a dentist. Corsodyl is also available as a spray (0.2%) and gel (1%) and used twice a day.

Povodine-iodine (Betadine)

Adults and children over 6 years of age should use a 10 mL dose four times a day, either undiluted or diluted with an equal volume of water. Because of its iodine content it should not be used for periods longer than 14 days because a significant amount of iodine is absorbed. Pregnant and breast-feeding women and patients with thyroid disorders should avoid its use.

Table 6.6
Practical prescribing: Summary of medicines for gingivitis

Name of medicine	Use in children	Likely side effects	Drug interactions of note	Patients in whom care should be exercised	Pregnancy and breast-feeding
Chlorhexidine	No age limit stated	Staining of teeth and tongue. Mild irritation	None	None	OK
Povidone-iodine	>6 years	None		Patients with thyroid disease	Avoid if possible
Hexetidine		Mild irritation or numbness of tongue		None	OK
Hydrogen peroxide		None			

HINTS AND TIPS BOX 6.3: IODINE MOUTHWASH

Regular use of iodine-containing mouthwashes	Regular use in pregnant women should be avoided because prolonged use can lead to iodine crossing the placental barrier and absorption by the foetus of a significant amount of iodine. This can result in hypothyroidism and goitre in the foetus and newborn
Dental flossing	Ideally people should floss once a day to remove plaque from between teeth. Correct technique is important otherwise gums can be traumatised. A piece of floss about eight inches long should be wrapped around the ends of the middle fingers of each hand leaving two to three inches between the first finger and thumb. The floss should be placed between two teeth and curved in to a 'C' shape around one tooth and slid up between the gum and tooth until resistance is felt then moved vertically up and down several times to remove plaque
Using fluoride	Fluoride has shown to reduce dental caries. In some parts of the UK drinking water contains measurable concentrations of fluoride and the need for fluoride toothpastes or supplementation is not needed. However, most people in Britain require fluoride supplementation, which is normally through toothpaste. Most packs of toothpaste state how many parts per million of fluoride the toothpaste contains; 500 ppm is a low level, 1000–1500 ppm is a high level. A low-dose toothpaste should be used for children under 7 to avoid dental fluorosis, which causes tooth discolouration. Oral fluoride supplements can also be given where fluoride in water is less than 0.7 parts per million

Hexetidine (Oraldene)

Adults and children over 6 years of age should use a 15 mL dose two or three times a day.

Hydrogen peroxide (e.g. Peroxyl)

Adults and children over 6 years of age should use 10 mL rinsed around the mouth up to four times a day.

Further reading

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Greenstein G. Povidone-iodine's effects and role in the management of periodontal diseases: a review. J Periodontol 1999;70:1397–405.

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Kelly M. Adult Dental Health Survey: Oral Health in the United Kingdom 1998. London: TSO, 2000.

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Maruniak J, Clark WB, Walker CB, et al. The effect of 3 mouthrinses on plaque and gingivitis development. J Clin Periodontol 1992;19:19–23.

Robinson PG, Deacon SA, Deery C, et al. Manual versus powered toothbrushing for oral health. Cochrane Database of Systematic Reviews 2005, issue 2.

Web sites

The British Dental Association: http://www.bda.org/

The British Fluoridation Society: http://www.bfsweb.org/

The British Dental Health Foundation: http://www.dentalhealth.org.uk/

The American Academy of Periodontology: http://www.perio.org/

Dyspepsia

Background

Confusion surrounds the terminology associated with upper abdominal symptoms and the term dyspepsia is used by different authors to mean different things. For example, the Rome II definition simply states: 'dyspepsia refers to pain or discomfort centred (that is around the midline) in the upper abdomen' (https://www.degnon.org/secure/romecriteria/romeii/). This should be compared with the British Society of Gastroenterology criteria, which are broader, and define dyspepsia as: 'any

symptom referable to the upper gastrointestinal tract . . . including upper abdominal pain or discomfort, heartburn, acid reflux, nausea and vomiting'.

It is therefore an umbrella term generally used by healthcare professionals to refer to a group of upper abdominal symptoms that arise from five main conditions:

- non-ulcer dyspepsia/functional dyspepsia (indigestion)
- gastro-oesophageal reflux disease (GORD)
- gastritis
- duodenal ulcers
- gastric ulcers

These five conditions represent 90% of dyspepsia cases presented to the GP.

In August 2004, The National Institute for Health and Clinical Excellence (NICE) issued clinical guidance on the management of dyspepsia in adults in primary care (http://www.nice.org.uk/page.aspx?o=CG017). In this section, specific reference is made to NICE guidance, especially in the management of dyspepsia.

Prevalence and epidemiology

The exact prevalence of dyspepsia is unknown. This is largely because of the number of people who self-medicate or do not report mild symptoms to their GP. However, it is clear that dyspepsia is extremely common. Between 25 and 40% of the general population in Western society are reported to suffer from dyspepsia and virtually everyone at some point in their lives will experience an episode of dyspepsia. Estimates suggest that 10% of people suffer on a weekly basis and that 5% of all GP consultations are for dyspepsia. The prevalence of dyspepsia is modestly higher in women than men.

Aetiology

The aetiology of dyspepsia differs depending on which condition the patient is suffering from. Lower oesophageal sphincter incompetence is the principal cause of GORD and is often caused by decreased muscle tone via medicines or overeating. Increased acid production results in inflammation of the stomach (gastritis) and is usually attributable to *Helicobacter pylori* infection, NSAIDs or acute alcohol indigestion. The presence of *H. pylori* is central to duodenal and gastric ulceration – *H. pylori* is present in 95% of duodenal ulcers and 70% of gastric ulcers. The mechanism by which it affects the aetiology of ulcers is still unclear but the bacteria is thought to secrete certain chemical factors resulting in gastric mucosal damage. Finally, when no specific cause can be found for a patient's symptoms the complaint is said to be non-ulcer dyspepsia. (Some authorities do not advocate the use of this term, preferring the term 'functional dyspepsia'.)

Arriving at a differential diagnosis

Overwhelmingly, patients who present with dyspepsia are likely to be suffering from GORD, gastritis or non-ulcer dyspepsia. Research has shown that even those patients who meet NICE guidelines for endoscopical investigation are found to have either gastritis/hiatus hernia (30%), oesphagitis (10 to 17%) or no abnormal findings (30%). It has also been reported that a medical practitioner with an average list size will only see one new case of oesophageal cancer and one new case of stomach cancer every 4 years. Despite this, a thorough medical and drug history should be taken to enable the community pharmacist to rule out serious pathology and diagnose dyspepsia. Alarm symptoms (see Trigger points indicative of referral) that would warrant further investigation are surprisingly common and it is important that these are referred to rule out serious pathology. A number of dyspepsia-specific questions should always be asked of the patient to aid in diagnosis (Table 6.7).

Clinical features of dyspepsia

Patients with dyspepsia present with a range of symptoms commonly involving:

- vague abdominal discomfort (aching) above the umbilicus associated with belching
- bloating
- flatulence
- a feeling of fullness
- nausea and/or vomiting
- heartburn

Although, dyspeptic symptoms are a poor predictor of disease severity or underlying pathology, retrosternal heartburn is the classic symptom of GORD.

Conditions to eliminate

Peptic ulceration

Ruling out peptic ulceration is probably the main consideration for community pharmacists when assessing patients with symptoms of dyspepsia. Ulcers are classed as either gastric or duodenal. They occur most commonly in patients aged between 30 and 50, although patients over the age of 60 account for 80% of deaths even though they only account for 15% of cases. Typically the patient will have well localised mid-epigastric pain described as 'constant', 'annoying' or 'gnawing/boring'. In gastric ulcers the pain comes on whenever the stomach is empty, usually 30 minutes after eating and is generally relieved by antacids or food and aggravated by alcohol and caffeine. Gastric ulcers are also more commonly associated with weight loss and GI bleeds than duodenal ulcers. Patients can experience weight loss of 5 to 10 kg and although this could indicate carcinoma, especially in

Table 6.7
Specific questions to ask the patient: Dyspepsia

Question	Relevance
Age	• The incidence of dyspepsia decreases with advancing age and therefore young adults are likely to suffer from dyspepsia with no specific pathological condition, unlike patients over 50 years of age, in whom a specific pathological condition becomes more common
Location	• Dyspepsia is experienced as pain above the umbilicus and centrally located (epigastric area). Pain below the umbilicus will not be due to dyspepsia • Pain experienced behind the sternum (breastbone) is likely to be heartburn • If the patient can point to a specific area of the abdomen then it is unlikely to be dyspepsia and could be caused by another GI condition, or could be musculoskeletal in origin
Nature of pain	• Pain associated with dyspepsia is described as aching or discomfort. Pain described as gnawing, sharp or stabbing is unlikely to be dyspepsia
Radiation	• Pain that radiates to other areas of the body is indicative of more serious pathology and the patient must be referred. The pain might be cardiovascular in origin, especially if the pain is felt down the inside aspect of the left arm
Severity	• Pain described as debilitating or severe must be referred to exclude more serious conditions
Associated symptoms	• Persistent vomiting with or without blood is suggestive of ulceration or even cancer and must be referred • Black and tarry stools indicate a bleed in the GI tract and must be referred
Aggravating or relieving factors	• Pain shortly after eating can indicate a gastric ulcer whereas pain 2 to 3 hours after eating can indicate a duodenal ulcer • Symptoms of dyspepsia are often brought on by certain types of food, for example, caffeine-containing products and spicy food
Social history	• Bouts of excessive drinking are commonly implicated in dyspepsia. Likewise, eating food on the move or too quickly is often the cause of the symptoms. A person's job is often a good clue to whether these are contributing to their symptoms

people aged over 40, on investigation a benign gastric ulcer is found most of the time. NSAID use is associated with a three- to four-fold increase in gastric ulcers.

Duodenal ulcers tend to be more consistent in symptom presentation. Pain occurs 2 to 3 hours after eating and pain that wakes a person at night is highly suggestive of duodenal ulcer. If ulcers are suspected referral to the GP is necessary as peptic ulcers can only be conclusively diagnosed by endoscopy.

Medicine-induced dyspepsia

A number of medicines can cause gastric irritation leading to or provoking GI discomfort or a decrease in oesophageal sphincter tone resulting in reflux. Patients should be questioned about medication, especially the use of aspirin and NSAIDs, which provoke dyspepsia in 25% of patients. Table 6.8 lists other medicines commonly implicated in causing dyspepsia.

Irritable bowel syndrome

Patients younger than 45 years who have uncomplicated dyspepsia and also lower abdominal pain and altered

Table 6.8
Medicines that commonly cause dyspepsia

Antibiotics, e.g. macrolides and tetracyclines
ACE inhibitors
Alcohol (in excess)
Bisphosphonates
Calcium antagonists
Iron
Metformin
Metronidazole
Nitrates
Oestrogens
Potassium supplements
Sibutramine
Steroids
Theophylline

bowel habits are likely to have irritable bowel syndrome (IBS). For further details on IBS see page 155.

Gastric carcinoma

Gastric carcinoma is the third most common GI malignancy after colorectal and pancreatic cancer. However, only 2% of patients who are referred by their GP for an endoscopy have malignancy. It is therefore a rare condition and community pharmacists are extremely unlikely to encounter a patient with carcinoma. One or more ALARM symptoms should be present plus symptoms such as nausea and vomiting.

Oesophageal carcinoma

In its early stages, oesophageal carcinoma might go unnoticed. Over time, however, as the oesophagus becomes constricted, patients will complain of difficulty in swallowing and experience a sensation of food sticking in the oesophagus. As the disease progresses weight loss becomes prominent despite the patient maintaining a good appetite.

Atypical angina

Not all cases of angina have classical textbook presentation of pain in the retrosternal area with radiation to the neck, back or left shoulder that is precipitated by temperature changes or exercise. Patients can complain of dyspepsia-like symptoms and feel generally unwell. These symptoms might be brought on by a heavy meal. In such cases antacids will fail to relieve symptoms and referral is needed.

Figure 6.10 will aid differentiation of the causes of dyspepsia.

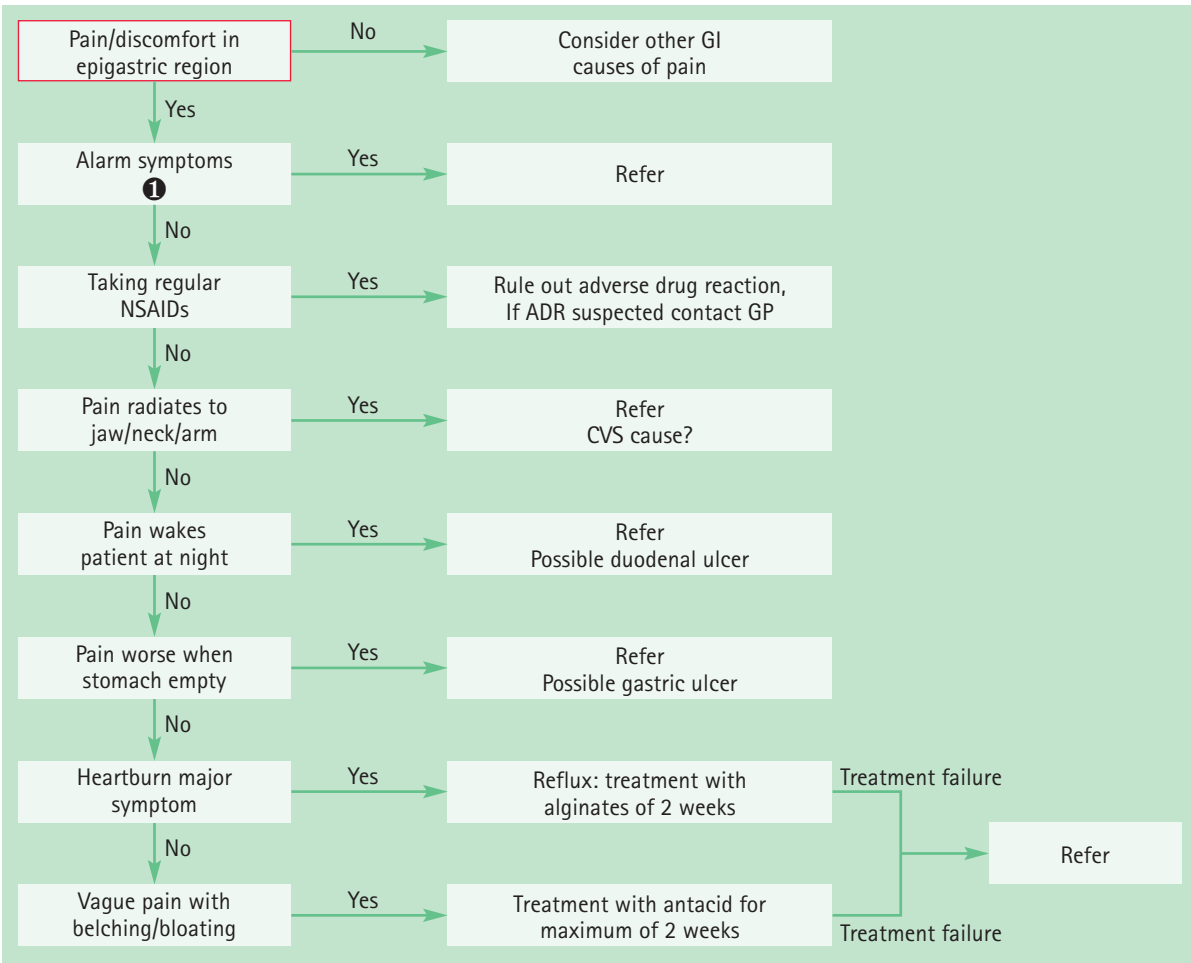

Fig. 6.10 Primer for differential diagnosis of dyspepsia

❶ **Alarm symptoms**
These include, anaemia (signs can include tiredness and pale complexion), loss of weight, anorexia, dark stools, difficulty in swallowing, vomiting blood.

TRIGGER POINTS indicative of referral: Dyspepsia

ALARM signs and symptoms

- Anaemia
- Loss of weight
- Anorexia
- Recent onset of progressive symptoms
- Melaena, dysphagia and haematemesis
- Pain described as severe, debilitating or that wakes the patient in the night
- Persistent vomiting (with or without blood)
- Referred pain
- Treatment failure

Evidence base for over-the-counter medication

In accordance with NICE guidelines the group of patients that should be treated by pharmacists are classed as having 'uninvestigated dyspepsia' (i.e. those that have not had endoscopical investigation). OTC treatment options consist of antacids, H_2 antagonists and proton pump inhibitors. Before treatment is instigated lifestyle advice should be given where appropriate. Although there is no strong evidence that dietary changes will lessen dyspepsia symptoms, a general healthier lifestyle will have wider health benefits. The patient should be assessed in terms of diet and physical activity:

1. Move to a lower fat diet
2. Alcohol intake to recommended levels (14 and 21 units/week for women and men, respectively)
3. Smoking cessation
4. Decrease weight
5. Reduce caffeine intake

It might also be possible to identify factors that precipitate or worsen symptoms. Commonly implicated foods that precipitate dyspepsia are spicy or fatty food, caffeine, chocolate and alcohol. Bending is also said to worsen symptoms.

Antacids

Antacids have been used for many decades to treat dyspepsia and have proven efficacy in neutralising stomach acid. However, the neutralising capacity of each antacid varies dependent on the metal salt used. In addition, the solubility of each metal salt differs, which affects their onset and duration of action. Sodium and potassium salts are the most highly soluble, which makes them quick but short-acting. Magnesium and aluminium salts are less soluble so have a slower onset but greater duration of action. Calcium salts have the advantage of being quick-acting yet have a prolonged action.

It is therefore commonplace for manufacturers to combine two or more antacid ingredients together to ensure a quick onset (generally sodium salts, e.g. sodium bicarbonate) and prolonged action (aluminium, magnesium or calcium salts).

Alginates

For patients suffering from heartburn and reflux an alginate product should be first-line treatment. When in contact with gastric acid the alginate precipitates out, forming a sponge-like matrix that floats on top of the stomach contents. Alginate preparations are also commonly combined with antacids (e.g. Gaviscon Advance) to help neutralise stomach acid. In clinical trials alginate-containing products have demonstrated superior symptom control compared to placebo and antacids. However, proton pump inhibitors and H_2 antagonists do have superior efficacy to alginates.

H_2 antagonists

Two H_2 antagonists are currently available OTC in the UK: ranitidine and famotidine. Cimetidine was also available OTC but was withdrawn by the manufacturer, presumably because of poor sales, and nizatidine has exemption from POM control but currently there is no product on the market.

H_2 antagonists are effective at POM doses but OTC licensed indications use lower doses. The question is, at these lower doses are they still effective? There is a paucity of publicly available trial data supporting their use at non-prescription doses. Famotidine appears to have the greatest body of accessible trial data. A number of trials have been conducted in patients suffering from heartburn and who regularly self-medicate with antacids. Famotidine was shown to be more effective than placebo and equally effective to antacids. No trials involving ranitidine could be found on public databases that involved patients taking OTC doses.

However, the inhibitory effects of OTC doses of ranitidine on gastric acid have been investigated in healthy volunteers. Trials showed conclusively that ranitidine, and its comparator drug famotidine, did significantly raise intragastric pH compared to placebo, although antacids (calcium carbonates) had a significantly quicker onset of action but with shorter duration. Despite ranitidine appearing to have no trial data relating to OTC doses, it is assumed that the product licence holders had enough evidence for their product to be granted a licence.

Proton pump inhibitors

Omeprazole is the first proton pump inhibitor (PPI) in the UK to be deregulated from POM control, although it is likely, in time, that others will follow suit. No specific OTC trials have been carried out with omeprazole.

However, a number of studies have used omeprazole 10 mg in head-to-head trials with antacid/alginate combinations and ranitidine for symptoms of dyspepsia/heartburn. Trials have shown omeprazole to be significantly more effective than both antacids and H_2 antagonists. The manufacturer's dosage schedule for OTC omeprazole is in line with current Prodigy guidelines for uninvestigated dyspepsia.

Summary

Antacids will work for the majority of people presenting at the pharmacy with mild dyspeptic symptoms. They can be used as first-line therapy unless heartburn predominates then an alginate or alginate/antacid combination can be used. H_2 antagonists appear to be equally effective to antacids but are considerably more expensive. Omeprazole has greater efficacy than all other OTC medicines for dyspepsia and should be considered first-line for those patients that suffer from moderate to severe or recurrent symptoms. Like H_2 antagonists it is expensive in comparison to simple antacids and might influence patient choice or pharmacist recommendation.

Practical prescribing and product selection

Prescribing information relating to the medicines used for dyspepsia reviewed in the section 'Evidence base for over-the-counter medication' is discussed and summarised in Table 6.9.

Antacids

The majority of marketed antacids are combination products containing two, three or even four constituents. The rationale for combining different salts together appears to be two-fold. First, to ensure the product has quick onset (containing sodium or calcium) and a long duration of action (containing magnesium, aluminium or calcium). Second, to minimise any side effects that might be experienced from the product. For example, magnesium salts tend to cause diarrhoea and aluminium salts con-

Table 6.9
Practical prescribing: Summary of medicines for dyspepsia

Name of medicine	Use in children	Likely side effects	Drug interactions of note	Patients in whom care should be exercised	Pregnancy and breast-feeding
Antacids					
Sodium only	>12 years	None	None	Patients with heart disease	OK
Calcium only		Constipation	Tetracyclines, quinolones, imidazoles, phenytoin, penicillamine and bisphosphonates	None	OK
Magnesium only		Diarrhoea			
Aluminium only		Constipation			
Alginates					
e.g. Gaviscon range, Gastrocote, Topal, Rennie liquid relief	>12 years*	None	None	Patients with heart disease	OK
H_2 antagonists					
Pepcid AC	>16 years	Diarrhoea, constipation, headache or rash	None	None	Experience has shown them to be OK
Zantac, Gavilast, Ranzac					
PPIs					
Omeprazole	>18 years	Headache, diarrhoea, constipation, nausea and vomiting, abdominal pain, flatulence	Azole antifungals, diazepam, fluvoxamine, cilostazol	None	Avoid

*Certain products such as Gaviscon, Gastrocote and Topal can be given to children but dyspepsia is unusual in children and it might be prudent to refer such patients to their GP.

HINTS AND TIPS BOX 6.4: ANTACIDS

Type of formulation?	Ideally, antacids should be given in the liquid form because the acid-neutralising capacity and speed of onset is greater than that of tablet formulations
Overuse of antacids	Misuse and chronic use of antacids will result in significant systemic absorption leading to various unwanted medical conditions. Milk-alkali syndrome has been reported with chronic abuse of calcium-containing antacids, as has osteomalacia with aluminium-containing products Antacid therapy should ideally not be longer than 2 weeks. If symptoms have not resolved in this time then other treatments and/or evaluation from the GP should be recommended
When is the best time to take antacids?	Antacids should be taken after food because gastric emptying is delayed in the presence of food. This allows antacids to exert their effect for up to 3 hours
Salt content	Be aware that some antacid preparations do contain significant amounts of salt – for example, Gaviscon Advance contains 4.6 mmol of sodium per 10 mL
The elderly	Avoid constipating products, as the elderly are prone to constipation
Possible solutions to minimise symptoms	Simple suggestions such as eating less but more often or eating smaller meals might help control symptoms. Eating late at night and lying flat at night should be avoided – a pillow should be used to prop the person up

stipation; however, if both are combined in the same product then neither side effect is noticed. Useful tips relating to antacids are given in Hints and Tips Box 6.4.

Antacids can affect the absorption of a number of medications via chelation and adsorption. Commonly affected medicines include tetracyclines, quinolones, imidazoles, phenytoin, penicillamine and bisphosphonates. In addition, the absorption of enteric-coated preparations can be affected due to antacids increasing the stomach pH. The majority of these interactions are easily overcome by leaving a minimum gap of 1 hour between the respective doses of each medicine.

Most patient groups can take antacids, although patients on salt-restricted diets (e.g. patients with coronary heart disease) should ideally avoid sodium-containing antacids. In addition, antacids should not be recommended in children because dyspepsia is unusual in children under 12 years. Indeed, most products are licensed for use only for children aged 12 and over. However, there are a few exceptions (e.g. Acidex, Gaviscon Advance, Topal), which have product licences for use in children.

Alginates (e.g. the Gaviscon range, Algicon)

Products containing alginates are combination preparations that contain an alginate with antacids. They are best given after each main meal and before bedtime, although they can be taken on a when-needed basis. They can be given during pregnancy and breast-feeding and to most patient groups but, as with antacids, patients on salt-restricted diets should ideally avoid sodium-containing alginate preparations. They are reported not to have any side effects or interactions with other medicines.

H_2 antagonists

Sales of H_2 antagonists are restricted to adults and children over the age of 16. They possess no clinically important drug interactions and side effects are rare. Safety concerns were raised on deregulation of H_2 antagonists about the potential to mask serious underlying conditions and the possibility of increased adverse reactions. These fears appear to have been unfounded as follow-up studies and post marketing surveillance has not shown any increase in risk associated with greater availability. Indeed, H_2 antagonists are now available as general sales list medicines. They have been used in pregnancy and breast-feeding, with ranitidine having been used most. Data suggest that there are no significant increases in any major malformations in pregnancy and they can be used while breast-feeding, and manufacturers of OTC products advise patients to speak to the doctor or pharmacist before taking.

Famotidine (PepcidTwo)

The dose for famotidine is 10 mg (one tablet) at the onset of symptoms; however, if symptoms persist an additional dose can be repeated after 1 hour. The maximum dose is 20 mg (two tablets) in 24 hours. A dose can be taken 1 hour prior to consuming food or drink that are known to bring on symptoms. PepcidTwo is a combination of famotidine, calcium carbonate and magnesium

hydroxide. The antacid component of the product provides quick onset of action helping to relieve symptoms before famotide exerts its action, which can take 2 hours.

Ranitidine (Zantac 75, Zantac Relief, Gavilast and Gavilast P, Ranzac)

Dosing for ranitidine is similar to famotidine in that one tablet should be taken straight away but if symptoms persist then a further tablet should be taken 1 hour later. The maximum dose is 300 mg (four tablets) in 24 hours. The General Sales List version of ranitidine, Zantac 75 Relief (and Ranzac), has a slightly different licence in that it cannot be used for prevention of heartburn and the maximum dose is only two tablets in 24 hours.

Omeprazole (Zanprol)

Zanprol is licensed for the relief of reflux-like symptoms (e.g. heartburn) associated with acid-related dyspepsia in patients aged over 18 years of age. The initial dose is two 10 mg tablets once daily. Once symptoms improve the dose can be reduced to one tablet (10 mg). If symptoms return then the dose can be stepped back up to 20 mg. Patients should be referred to their GP if symptoms do not resolve in 2 weeks or they need to use omeprazole for more than 4 weeks continuously. Omeprazole can cause a number of common side effects (>1 in 100), which include headache, diarrhoea, constipation, abdominal pain, nausea and vomiting and flatulence. Drug interactions with omeprazole are possible because it is metabolised in the liver by cytochrome P450 isoenzymes. These include 'azole' antifungals (decrease in azole bioavailability), diazepam (enhanced diazepam side effects), fluvoxamine (increased omeprazole levels) and cilostazol (increased cilostazol levels – UK manufacturers advise against co-administration). Other interactions listed in the manufacturer's literature include phenytoin and warfarin but their clinical significance appears low.

It appears to be safe in pregnancy and is excreted in only small amounts in breast milk. It is not contraindicated when used as a POM medicine; however, for pharmacy use it is not recommended.

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Web sites

British Society of Gastroenterology: http://www.bsg.org.uk/

NPC Resource on dyspepsia: http://www.npc.co.uk/dyspepsia_addtl_resources.htm

CORE: http://www.corecharity.org.uk/

American Gastroenterological Association: http://www.gastro.org/

NICE Guidance on dyspepsia: http://www.nice.org.uk/page.aspx?o=218381

On-line article on GORD from The Prescriber (August 2004): http://www.escriber.com/Prescriber/Features.asp?ID=854&tGroupID=6&tAction=View

Diarrhoea

Background

Diarrhoea can be defined as an increase in frequency of the passage of soft or watery stools relative to the usual bowel habit for that individual. It is not a disease but a sign of an underlying problem such as an infection or gastrointestinal disorder. It can be classed as acute (less than 7 days), persistent (more than 14 days) or chronic (lasting longer than a month). Most patients will present to the pharmacy with a self-diagnosis of acute diarrhoea. It is necessary to confirm this self-diagnosis because patients' interpretations of their symptoms might not match up with the medical definition of diarrhoea.

Prevalence and epidemiology

The exact prevalence and epidemiology of diarrhoea is not well known. This is probably due to the number of patients who do not seek care or who self-medicate.

However, acute diarrhoea does generate high GP consultation rates. For example, diarrhoeal illness has been reported as being the second most common medical problem in American households. It has been reported that children under the age of 5 years have between one and three bouts of diarrhoea per year and adults, on average, just under one episode of diarrhoea per year. Many of these cases are thought to be food related.

Aetiology

The aetiology of diarrhoea depends on its cause. Acute gastroenteritis, the most common cause of diarrhoea in all age groups, is usually viral in origin. In the UK rotavirus and small round structured virus (SRSV) are the most commonly identified causes of gastroenteritis in children, and in adults, *Campylobacter* followed by rotavirus are the most common. Other pathogens identified include *E. coli*, *Salmonella*, *Shigella*, viruses such as adenovirus and the protozoa *Cryptosporidium* and *Giardia*. Viral causes tend to cause diarrhoea by blunting of the villi of the upper small intestine decreasing the absorptive surface. Bacterial causes of diarrhoea are normally a result of eating contaminated food or drink and cause diarrhoea by a number of mechanisms. For example, enterotoxigenic *E. coli* produce enterotoxins that affect gut function with secretion and loss of fluids; enteropathogenic *E. coli* interferes with normal mucosal function; and enteroinvasive *E. coli*, *Shigella* and *Salmonella* species cause injury to the mucosa of the small intestine and deeper tissues.

Other organisms, for example *Staphylococcus aureus* and *Bacillus cereus*, produce preformed enterotoxins, which on ingestion stimulate the active secretion of electrolytes into the intestinal lumen.

Arriving at a differential diagnosis

Acute diarrhoea is rarely life-threatening. The most common causes of diarrhoea are viral or bacterial infection and the community pharmacist can appropriately manage the vast majority of cases. The main priority is identifying those patients that need referral and how quickly they need to be referred. Dehydration is the main complicating factor, especially in the very young and very old. Questions aimed at establishing the frequency, fluidity and nature of the stools should enable a patient self-diagnosis to be rejected or confirmed. A number of diarrhoea-specific questions should always be asked of the patient to aid in diagnosis (Table 6.10).

Clinical features of acute diarrhoea

Symptoms are normally rapid in onset, with the patient having a history of prior good health. Nausea and vomiting might be present prior to or during the bout of acute

Table 6.10
Specific questions to ask the patient: Diarrhoea

Question	Relevance
Frequency and nature of the stools	• Patients with acute self-limiting diarrhoea will be passing watery stools more frequently than normal • Diarrhoea associated with blood and mucus (dysentery) requires referral to eliminate invasive infection such as *Shigella, Campylobacter, Salmonella* or *E. coli* O157 • Bloody stools are also associated with conditions such as inflammatory bowel disease
Periodicity	• A history of recurrent diarrhoea of no known cause should be referred for further investigation
Duration	• A person who presents with a history of chronic diarrhoea should be referred. The most frequent causes of chronic diarrhoea are IBS, inflammatory disease and colon cancer
Onset of symptoms	• Ingestion of bacterial pathogens can give rise to symptoms in a matter of a few hours (toxin-producing bacteria) after eating contaminated food or up to 3 days later. It is therefore important to ask about food consumption over the last few days, establish if anyone else ate the same food and to check the status of his or her health
Timing of diarrhoea	• Patients who experience diarrhoea first thing in the morning might well have underlying pathology such as IBS • Nocturnal diarrhoea is often associated with inflammatory bowel disease
Recent change of diet	• Changes in diet can cause changes to bowel function, for example, when away on holiday. If the person has recently been to a non-Western country then giardiasis is a possibility
Signs of dehydration	• Mild (<5%) dehydration can be vague but may include tiredness, anorexia, nausea and light-headedness • Moderate (5 to 10%) dehydration is characterised by dry mouth, sunken eyes, decreased urine output, moderate thirst and decreased skin turgor (pinch test of 1 to 2 seconds or longer)

diarrhoea. Abdominal cramping, flatulence and tenderness are also often present. If rotavirus is the cause the patient might also experience viral prodromal symptoms such as cough and cold. Acute infective diarrhoea is usually watery in nature with no blood present. Complete resolution of symptoms should be observed in 2 to 4 days. However, diarrhoea caused by the rotavirus can persist for longer.

Conditions to eliminate

Giardiasis

Giardiasis, a protozoan infection of the small intestine, is contracted through drinking contaminated water. It is an uncommon cause of diarrhoea in Western society. However, with more people taking exotic foreign holidays, enquiry about recent travel should be made. The patient will present with watery and foul-smelling diarrhoea accompanied by symptoms of bloating, flatulence and epigastric pain. If giardiasis is suspected the patient must be referred to the GP quickly for confirmation and appropriate antibiotic treatment.

Irritable bowel syndrome

Patients younger than 45 with lower abdominal pain and a history of alternating diarrhoea and constipation are likely to have IBS. For further details on IBS see page 155.

Medicine-induced diarrhoea

Many medicines – both POM and OTC – can induce diarrhoea (Table 6.11). If medication is suspected as the cause of the diarrhoea the GP should be contacted and an alternative suggested.

Ulcerative colitis and Crohn's disease

Both conditions are characterised by chronic inflammation at various sites in the GI tract and follow periods of remission and relapse. They can affect any age group, although peak incidence is between 20 and 30 years of age. In mild cases of both conditions, diarrhoea is one of the major presenting symptoms, although blood in the stool is usually present. Patients might also find that they have urgency, nocturnal diarrhoea and early morning rushes. In the acute phase patients will appear unwell and have malaise.

Malabsorption syndromes

Lactose intolerance is often diagnosed in infants under 1 year old. In addition to more frequent loose bowel movements symptoms such as fever, vomiting, perianal excoriation and a failure to gain weight might occur.

Coeliac disease has a bimodal incidence: first, in early infancy when cereals become a major constituent of the diet, and second, during the fourth and fifth decades. Steatorrhoea (fatty stools) is common and might be observed by the patient as frothy or floating stools in the toilet pan. Bloating and weight loss in the presence of a normal appetite might also be observed.

Faecal impaction

Faecal impaction is most commonly seen in the elderly and those with poor mobility. Patients might present with continuous soiling as a result of liquid passing around hard stools and mistakenly believe they have diarrhoea. On questioning, the patient might describe the passage of regular poorly formed hard stools that are difficult to pass. Referral is needed as manual removal of the faeces is often necessary.

Colorectal cancer

Any middle-aged patient presenting with a long-standing change of bowel habit must be viewed with suspicion. Persistent diarrhoea accompanied by a feeling that the bowel has not really been emptied is suggestive of neoplasm. This is especially true if weight loss is also present.

Figure 6.11 will aid differentiation of diarrhoeal cases that require referral.

TRIGGER POINTS indicative of referral: Diarrhoea

- Change in bowel (long term) habit in patients over 50
- Diarrhoea following recent travel to tropical or subtropical climate
- Duration longer than 2 to 3 days in children and elderly
- Patients unable to drink fluids
- Presence of blood or mucous in the stool
- Signs of dehydration
- Severe abdominal pain
- Steatorrhoea
- Suspected faecal impaction in the elderly

Evidence base for over-the-counter medication

Acute infectious diarrhoea still remains one of the leading causes of death in developing countries, despite advances in its treatment. In developed and Western countries diarrhoeal disease is primarily of economic and socially disruptive significance. Goals of OTC treatment in the UK are therefore concentrated on relief of symptoms.

Table 6.11
Medicines known to cause diarrhoea (defined as >1% from manufacturers' data)

α-blocker	Prazosin
ACEI & angiotension II antagonist	Lisinopril, perindopril, telmisartan
Acetylcholinesterase inhibitor	Donepezil, galantamine, rivastigmine
Antacid	Magnesium salts
Antibacterial	All
Antidiabetic	Metformin, acarbose
Antidepressant	SSRIs, clomipramine, venlafaxine
Anti-emetic	Aprepitant, dolasetron
Anti-epileptic	Carbamazepine, oxcarbamazepine, tiagabine, zonisamide, pregabalin, levtiracetam
Antifungal	Caspofungilin, fluconazole, flucytosine, nystatin (in large doses), terbinafine, voriconazole
Antimalarial	Mefloquine
Antiprotozoal	Metronidazole, sodium stibogluconate
Antipsychotic	Arirpiprazole
Antiviral	Abacavir, emtricitabine, stavudine, tenofovir, zalcitabine, zidovudine, amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, saquinavir, efavirinez, ganciclovir, valganciclovir, adefovir, oseltamivir, ribavrin, fosamprenavir
β-blocker	Bisoprolol, carvedilol, nebivolol
Bisphosphonate	Alendronic acid, disodium etidronate, ibandronic acid, risedronate, sodium clodronate, disodium pamidronate, tiludronic acid
Cytokine inhibitor	Adalimumab, infliximab
Cytotoxic	All classes of cytotoxics
Dopaminergic	Levodopa, entacapone
Growth hormone antagonist	Pegvisomant
Immunosuppressant	Ciclosporin, mycophenolate, leflunomide
NSAID	All
Ulcer healing	Proton pump inhibitors
Vaccines	Pediacel, haemophilus, meningococcal
Miscellaneous	Calcitonin, strontium ranelate, colchicines, dantrolene, olsalazine, anagrelide, nicotinic acid, pancreatin, eplerenone, acamprosate

Oral rehydration solution (ORS)

ORS represents one of the major advances in medicine. It has proven to be a simple highly effective treatment, which has decreased mortality and morbidity associated with acute diarrhoea in developing countries. The formula recommended by the World Health Organization (WHO) contains glucose (75 mmol/L), sodium (75 mmol/L), potassium (20 mmol/L), chloride (65 mmol/L) and citrate (10 mmol/L) in an almost isotonic fluid. Until recently, the WHO oral rehydration solution contained 90 mmol/L sodium but a systematic review (Hahn et al 2002) concluded that ORSs with a reduced osmolarity compared to the standard WHO formula were associated with fewer

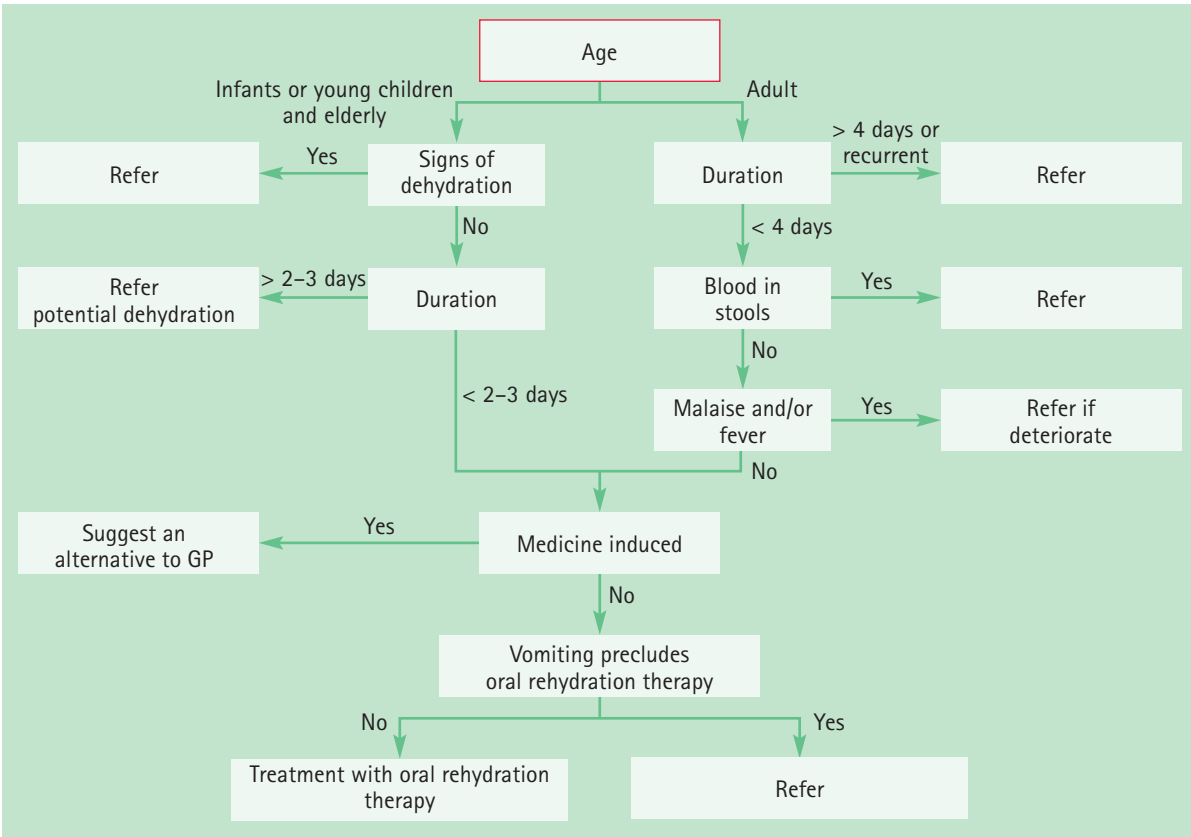

Fig. 6.11 Primer for differential diagnosis of diarrhoea

complications in children with mild to moderate diarrhoea. Based on this, and other findings, the WHO oral rehydration solution now has a reduced osmolarity of 245 mm/L, which contains 75 mmol of sodium. A number of similar preparations are available commercially in the form of sachets that require reconstitution in clean water before use; however, commercially available solutions in the UK still contain lower sodium concentrations as diarrhoea tends to be isotonic and therefore replacement of large quantities of sodium is less important.

Rice-based ORS

In many developing countries a glucose substitute was added to electrolytes because of glucose unavailability. These products were found to be quite successful. Clinical trials have subsequently shown rice-based ORS to be highly efficacious, well tolerated and potentially more effective than conventional ORS.

Loperamide

Loperamide is a synthetic opioid analogue and is thought to exert its action via opiate receptors slowing intestinal tract time and increasing the capacity of the gut. It has been extensively researched, with many published trials investigating its effectiveness in acute infectious diarrhoea. The majority of well-designed double-blind placebo-controlled trials have consistently shown it to be significantly better than placebo and comparable to diphenoxylate.

Bismuth subsalicylate

Bismuth-containing products have been used for many decades. The use of bismuth subsalicylate has declined over time as other products have become more popular. However, it has been shown to be effective in treating traveller's diarrhoea. A review paper by Steffen (1990) concluded that bismuth subsalicylate was clinically superior to placebo, decreasing the number of unformed stools and increasing the number of patients who were symptom-free. However, two of the trials reviewed showed bismuth subsalicylate to be significantly slower in symptom resolution than its comparator drug loperamide.

Kaolin and morphine

The constipating side effect of opioid analgesics can be used to treat diarrhoea. However, kaolin and morphine products have no evidence of efficacy and should not be recommended. This remains a popular home remedy, especially with the elderly.

Rotavirus vaccine

In 2006, two new oral vaccines (Rotarix and RotaTeq) were licensed by the European Medicines Agency and the US Food and Drug Administration. Clinical trials have shown them to protect against the most common circulating strains of rotavirus (G1 and G3) and the emerging G9 strain. The vaccine can be co-administered with other childhood vaccinations according to manufacturers but currently it is not part of the UK childhood vaccination programme.

Summary

As diarrhoea results in fluid and electrolyte loss it is important to re-establish normal fluid balance and so ORS is first-line treatment for all age groups, especially children and the frail elderly. Loperamide is a useful adjunct in reducing the number of bowel movements but should be reserved for those patients who will find it inconvenient to have to go to the toilet.

Practical prescribing and product selection

Prescribing information relating to the medicines used for diarrhoea reviewed in the section 'Evidence base for over-the-counter medicine' is discussed and summarised in Table 6.12; useful tips relating to patients presenting with diarrhoea are given in Hints and Tips Box 6.5.

ORS (Dioralyte, Dioralyte Relief (rice-based), Electrolade, Rapolyte)

ORS can be given to all patient groups and has no side effects or drug interactions. The volume of solution

Table 6.12
Practical prescribing: Summary of medicines for diarrhoea

Name of medicine	Use in children	Likely side effects	Drug interactions of note	Patients in whom care should be exercised	Pregnancy and breast-feeding
ORS	Infant upwards	None	None	None	OK
Loperamide	>12 years	Abdominal cramps, nausea, vomiting, tiredness	None	None	OK
Bismuth	>16 years	Black stools or tongue	Quinolone antibiotics	None	Avoid if possible
Morphine salts					
Kaolin and morphine	>12 years	None	None	None	OK
Diocalm	>6 years				

HINTS AND TIPS BOX 6.5: DIARRHOEA

Reconstitution of ORS	All proprietary sachets require 200 mL of water per sachet to reconstitute Different brands come in different flavours, e.g. Dioralyte – blackcurrant and citrus Dioralyte Relief – apricot, raspberry or blackcurrant Rapolyte – blackcurrant or raspberry Electrolade – banana, blackcurrant, lemon and lime and orange Once reconstituted ORS must be stored in the fridge and drunk within 24 hours
Rough guidelines for referral for children	<1 year old: refer if duration >1 day <3 years old: refer if duration >2 days >3 years old: refer if duration >3 days
Kaolin and morphine	Subject to abuse. Store out of sight
Alternative to ORS	Patients can be advised to increase their intake of fluids, particularly fruit juices with their glucose and potassium content, and soups because of their sodium chloride content

given is dependent on how much fluid is lost. As infants and the elderly are more at risk of developing dehydration they should be encouraged to drink as much ORS as possible. In adults, 2 L of ORS should be given in the first 24 hours, followed by unrestricted normal fluids with 200 mL of rehydration solution per loose stool or vomit. The solution is best sipped every 5 to 10 minutes rather than drunk in large quantities less frequently. In infants, 1 to 1½ times the usual feed volume should be given.

Loperamide (e.g. Arret, Diocalm Ultra, Diah-Limit, Imodium)

The dose is two capsules immediately, followed by one capsule after each further bout of diarrhoea. It has minimal CNS side effects, although CNS depressant effects and respiratory depression have been reported at high doses. OTC doses are therefore limited to 16 mg a day and cannot be used in children under 12. The excellent safety record of loperamide has seen it granted General Sales List status, although abdominal cramps, nausea, vomiting, tiredness, drowsiness, dizziness and dry mouth have been reported. Loperamide is also available as dispersible tablets, melt-tabs and liquid (the Imodium range of products).

Bismuth (Pepto-Bismol 87.6 mg/5 mL bismuth subsalicylate)

Pepto-Bismol should only be given to people over the age of 16. This age limit has been set by the company due to the association of taking aspirin and Reye's syndrome. The dose is 30 mL taken every 30 minutes to 1 hour when needed, with a maximum of eight doses in 24 hours. Bismuth subsalicylate is well tolerated and has a favourable side effect profile, although black stools are commonly observed (caused by unabsorbed bismuth compound). Occasional use is not known to cause problems during pregnancy but the manufacturers state it should not be taken during pregnancy. Bismuth can decrease the bioavailability of quinolone antibiotics therefore a minimum 2-hour gap should be left between doses of each medicine.

Morphine (e.g. kaolin and morphine, Diocalm Dual Action)

Morphine is generally well tolerated at OTC doses, with no side effects reported. The products can be given to all patient groups, including pregnant women. There are no drug interactions of note.

Kaolin and morphine

If kaolin and morphine is prescribed then it can only be given to adults and children over the age of 12. The normal dose is 10 mL every 4 hours.

Diocalm Dual Action

Adults and children over the age of 12 should take two tablets every 2 to 4 hours as required and children aged 6 to 12 years should take half the adult dose.

Further reading

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Web sites

General information on diarrhoea: http://www.diarrhoea.org/index.html

National Association for Colitis and Crohn's disease (NACC): http://www.nacc.org.uk

Clinical signs and diagnosis of dehydration: http://www.pediatrics.org/cgi/content/full/99/5/e6.

Constipation

Background

Constipation, like diarrhoea, means different things to different people. Constipation arises when the patient experiences a reduction in their normal bowel habit accompanied with more difficult defecation and/or hard stools. In Western populations 90% of people defecate between three times a day and once every three days. However, many people still believe that anything other than one bowel movement a day is abnormal.

Prevalence and epidemiology

Constipation is very common. It occurs in all age groups but is especially common in the elderly. It has been estimated that 25 to 40% of all people over the age of 65 have constipation. The majority of the elderly have normal frequency of bowel movements but strain at stool. This is probably a result of sedentary lifestyle, a decreased fluid intake, poor nutrition, avoidance of fibrous foods and chronic illness. Women are two to three times more likely to suffer from constipation than men and 40% of women in late pregnancy experience constipation.

Aetiology

The normal function of the large intestine is to remove water and various salts from the colon, drying and expulsion of the faeces. Any process that facilitates water resorption will generally lead to constipation. The commonest cause of constipation is an increase in intestinal tract transit time of food, which allows greater water resorption from the large bowel leading to harder stools that are more difficult to pass. This is most frequently caused by a deficiency in dietary fibre, a change in lifestyle and/or environment and medication. Occasionally, patients ignore the defactory reflex as it may be inconvenient for them to defecate.

Arriving at a differential diagnosis

The first thing a pharmacist should do is to establish the patient's current bowel habit compared to normal. This should establish if the patient is suffering from constipation. Questioning should then concentrate on determining the cause because constipation is a symptom and not a disease and can be caused by many different conditions. Constipation does not usually have sinister pathology and the commonest cause in the vast majority of non-elderly adults will be a lack of dietary fibre. However, constipation can be caused by medication and many disease states including neurological disorders (e.g. multiple sclerosis, Parkinson's disease), metabolic and endocrine conditions (diabetes, hypothroidism) and neoplasm. A number of constipation-specific questions should always be asked of the patient to aid in diagnosis (Table 6.13).

Clinical features of constipation

Besides the inability to defecate, patients might also have abdominal discomfort and bloating. In children, parents might also notice the child is more irritable and have a decreased appetite. Specks of blood in the toilet pan might be present and are usually due to straining at stool.

Table 6.13
Specific questions to ask the patient: Constipation

Question	Relevance
Change of diet or routine	Constipation usually has a social or behavioural cause. There will usually be some event that has precipitated the onset of symptoms
Pain on defecation	Associated pain when going to the toilet is usually due to a local anorectal problem. Constipation is often secondary to the suppression of defecation because it induces pain. These cases are best referred for physical examination
Presence of blood	Bright red specks in the toilet or smears on toilet tissue suggest haemorrhoids or a tear in the anal canal (fissure). However, if blood is mixed in the stool (melaena) then referral to the GP is necessary. A stool that appears black and tarry is suggestive of an upper GI bleed
Duration (chronic or recent?)	Constipation lasting 6 weeks or more is said to be chronic. If a patient suffers from long-standing constipation and has been previously seen by the GP then treatment could be given. However, cases of more than 14 days with no identifiable cause or previous investigation by the GP should be referred
Lifestyle changes	Changes in job or marital status can precipitate depressive illness that can manifest with physiological symptoms such as constipation

In the vast majority of cases blood in the stool does not indicate sinister pathology. Those patients presenting with acute constipation with no other symptoms apart from very small amounts of bright red blood can be managed in the pharmacy; however, if blood loss is substantial (stools appear tarry, red or black) or the patient has other associated symptoms such as malaise and abdominal distension and is over 40 years old then referral is needed.

Conditions to eliminate

Medicine-induced constipation

Many medicines are known to cause constipation. Most exert their action by decreasing gut motility, although opioids tend to raise sphincter tone and reduce sensitivity to rectal distension. A detailed medication history should always be sought from the patient and Table 6.14 lists the commonly implicated medicines that cause constipation.

Irritable bowel syndrome

Patients younger than 45 with lower abdominal pain and a history of alternating diarrhoea and constipation are likely to have IBS. For further details on IBS see page 155.

Pregnancy

Constipation is common in pregnancy, especially in the third trimester. A combination of increased circulating progestogen, displacement of the uterus against the colon by the foetus, decreased mobility and iron supplementation all contribute to an increased incidence of constipation whilst pregnant. Most patients complain of hard stools rather than a decrease in bowel movements. If a laxative is used a bulk-forming laxative should be recommended.

Functional causes in children

Constipation in children is common and the cause can be varied. Constipation is not normally a result of organic disease but stems from poor diet or a traumatic experience associated with defecation, for example, unwillingness to defecate due to association of prior pain on defecation.

Depression

Upwards of 20% of the population will suffer from depression at some time. Many will present with physical rather than emotional symptoms. It has been reported that a third of all patients suffering from depression present with gastrointestinal complaints in a primary care setting. It is important to ensure that a social history is taken.

Colorectal cancer

Colorectal carcinomas are rare in patients under the age of 40. However, the incidence of carcinoma increases with increasing age and any patient over the age of 40 presenting for the first time with a marked change in bowel habit should be referred. Sexes appear to be equally affected. The patient might complain of abdominal pain, rectal bleeding and tenesmus. Weight loss – a classical textbook sign of colon cancer – is common but observed only in the latter stages of the disease. Therefore, a patient is unlikely to have noticed marked weight loss when visiting a pharmacy early in disease progression.

Hypothyroidism

The signs and symptoms of hypothyroidism are often subtle and insidious in onset. Patients might experience weight gain, lethargy, cold intolerance, coarse hair and dry skin as well as constipation. Hypothyroidism affects ten times more women than men and peak incidence is in the fifth or sixth decade. Constipation is often less pronounced than lethargy and cold intolerance.

Figure 6.12 will aid differentiation between common causes of constipation and more serious causes.

TRIGGER POINTS indicative of referral: Constipation

- Blood in stool
- Greater than 14 days' duration with no identifiable cause
- Pain on defecation causing patient to suppress defecatory reflex
- Patients aged over 40 with sudden change in bowel habits with no obvious cause
- Suspected depression
- Tiredness

Evidence base for over-the-counter medication

For uncomplicated constipation, non-drug treatment is advocated as first-line treatment for all patient groups as simple dietary and lifestyle modifications (increasing exercise) will relieve the majority of acute cases of constipation. Advice includes increasing fluid and fibre intake. Dietary fibre increases stool bulk, stool water content and colonic bacterial load. Fibre intake should be increased to approximately 30 g day in the form of fruit, vegetables, cereals, grain foods and wholemeal bread. It is important to remind patients that adequate fluid intake (2 L per day) is needed when following a high-fibre diet and patients might experience excessive gas production, colicky abdominal pain and bloating. Effects of a high-fibre diet are usually seen in 3 to 5 days.

Table 6.14
Medicines known to cause constipation (defined as >1% from manufacturers' data)

α-blocker	Prazosin
Antacid	Aluminium and calcium salts
Anticholinergic	Trihexyphenidyl, hyoscine, oxybutynin, procyclidine, tolterodine
Antidepressant	Tricyclics, SSRIs, reboxetine, venlafaxine, duloxetine, mirtazepine
Anti-emetic	Palonosetron, dolasetron, aprepitant
Anti-epileptic	Carbamazepine, oxcarbazepine
Antipsychotic	Phenothiazines, haloperidol, pimozide and atypical antipsychotics such as amisulpride, arirpiprazole, olanzapine, quetiapine, risperidone, zotepine, clozapine
Antiviral	Foscarnet
β-blocker	Oxprenolol, bisoprolol, nebivolol; other β-blockers tend to cause constipation more rarely
Bisphosphonate	Alendronic acid
CNS stimulant	Atomoxetine
Calcium channel blocker	Diltiazem, verapamil
Cytotoxic	Bortezomib, buserelin, cladribine, docetaxel, doxorubicin, exemestane, gemcitabine, irinotecan, mitozantrone, pentostatin, temozolomide, topotecan, vinblastine, vincristine, vindesine, vinorelbine
Dopaminergic	Amantadine, bromocriptine, carbegolide, entacapone, tolcapone, levodopa, pergolide, pramipexole, quinagolide
Growth hormone antagonist	Pegvisomant
Immunosuppressant	Basiliximab, mycophenolate, tacrolimus
Lipid-lowering agent	Colestyramine, colestipol, rosuvastatin, atorvastatin (other statins reported as uncommon), gemfibrozil
Iron	Ferrous sulphate
Metabolic disorders	Miglustat
Muscle relaxant	Baclofen
NSAID	Meloxicam; other NSAIDs, e.g. aceclofenac, and Cox-2 inhibitors reported as uncommon
Smoking cessation	Bupropion
Opioid analgesic	All opioid analgesics and derivatives
Ulcer healing	Proton pump inhibitors, sucralfate

If medication is required, four classes of OTC laxatives are available: bulk-forming agents, stimulants, osmotic laxatives and stool softeners. Despite their widespread use surprisingly few well-designed trials have substantiated clinical efficacy.

A systematic review by Tramonte in 1997 identified 36 trials involving 1815 participants that met their inclusion criteria and involved 25 different laxatives representing all four classes of laxative. Twenty of the trials compared laxative against placebo or regular diet, 13 of which demonstrated statistically significant increases in bowel movement. The remaining 16 trials compared different types of laxatives with each other. The review concluded that laxatives do increase the number of bowel movements and in 9 of 11 trials studying overall symptom control, laxatives did perform significantly better than placebo. Unfortunately, because of a lack of comparative trial data, the review could not conclude which laxative was most efficacious. A further review of laxative effect in elderly patients suffering with chronic constipation

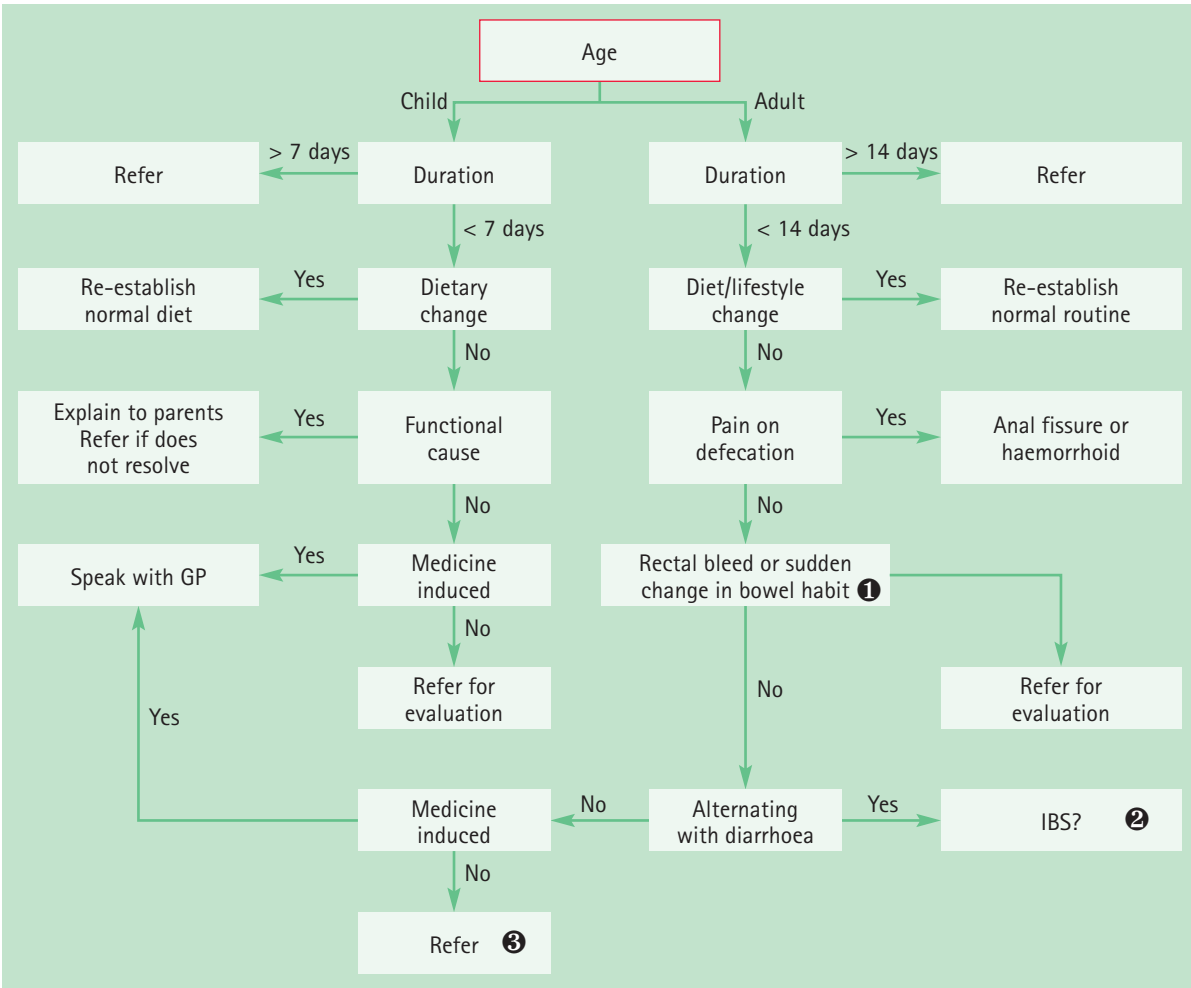

Fig. 6.12 Primer for differential diagnosis of constipation

❶ Patients with unexplained constipation of recent onset accompanied with rectal bleeding should be referred for further investigation; most likely a colonoscopy or sigmoidoscopy and stool culture to eliminate carcinoma

❷ See Fig. 6.13 for primer for differential diagnosis of IBS.

❸ If no obvious cause of constipation can be found referral to the GP is needed for further evaluation.

also failed to determine superior clinical effect between laxative classes. The findings from the Tramonte paper were reviewed in 2005 by the Centre for Reviews and Dissemination, which supported them.

Summary

It appears from the evidence that laxatives do work, but deciding on which laxative to give a patient cannot be made on an evidence-based approach. Other factors will need to be considered such as the patients' status, side effect profile of the medicine and its cost.

Practical prescribing and product selection

Prescribing information relating to the medicines used for constipation reviewed in the section 'Evidence base for over-the-counter medication' is discussed and summarised in Table 6.15; useful tips relating to these medicines are given in Hints and Tips Box 6.6.

The BNF (edition 55) recommends that laxatives should be prescribed by healthcare professionals experienced in the management of constipation in children. Products OTC can be used in younger age groups but in accordance with good practice those children younger than 6 years old who have failed to respond to dietary intervention should be referred to their GP. The text below does, however, make reference to dosing in children younger than 6.

Bulk-forming laxatives (e.g. ispaghula husk, methylcellulose and sterculia)

Bulk-forming laxatives exert their effect by mimicking increased fibre consumption swelling in the bowel and increasing faecal mass. In addition, they also encourage

Table 6.15
Practical prescribing: Summary of medicines for constipation

Name of medicine	Use in children	Likely side effects	Drug interactions of note	Patients in whom care should be exercised	Pregnancy and breast-feeding
Bulk-forming laxatives					
Ispaghula husk	>6 years	Flatulence and abdominal bloating	None	None	OK
Methylcellulose	Not recommended				
Sterculia	>6 years				
Stimulant laxatives					
Senna	>2 years	Abdominal pain	None	None	OK, but use other laxatives in preference to stimulants in pregnancy
Glycerol	Infant upwards				
Sodium picosulphate	>4 years				
Bisacodyl	>4 years				
Osmotic laxatives					
Lactulose	Infant upwards	Flatulence, abdominal pain and colic	None	None	OK
Magnesium hydroxide	Not recommended				
Stool softeners					
Docusate	>6 months	None reported	None	None	OK

the proliferation of colonic bacteria and this helps further increase faecal bulk and stool softness. Patients should be advised to increase their fluid intake while taking bulk-forming medicines. Their effect is usually seen in 12 to 36 hours but can take as long as 72 hours. Side effects commonly experienced include flatulence and abdominal distension. They are well tolerated in pregnancy and breast-feeding and have no teratogenic effects. They appear to have no drug interactions of any note.

Ispaghula husk

Ispaghula husk is widely available as either granules (Fibrelief, Fybogel, Isogel, Ispagel and Senokot Hi-fibre) or powder (Regulan). All have to be reconstituted with water prior to taking. The dose for adults and children over 12 years old can range from one to six sachets a day depending on the brand used and the severity of the condition. Fybogel is probably the most familiar branded product used OTC in the UK – adults should take one sachet or two level 5 mL spoonfuls twice a day and for children aged between 6 and 12 years, a half to one 5 mL spoonful.

Methylcellulose (Celevac)

Methylcellulose is only available as Celevac tablets. The product is only recommended for adults and the dose is three to six tablets twice daily. Each dose should be taken with at least 300 mL of liquid.

Sterculia (Normacol and Normacol Plus granules or sachets)

Both products contain 62% sterculia but Normacol Plus also contains 8% frangula. The dose for both products is the same. Adults and children over 12 should take either one or two sachets or heaped 5 mL spoonfuls, once or twice daily after meals. For children aged between 6 and 12 the dose is half that of the adult dose.

The granules should be placed dry on the tongue and swallowed immediately with plenty of water or a cool drink. They can also be sprinkled onto, and taken with, soft food such as yoghurt.

Stimulant laxatives (e.g. bisacodyl, glycerol, senna, sodium picosulfate)

Stimulant laxatives increase GI motility by directly stimulating colonic nerves. It is this action that, presumably, causes abdominal pain and is the main side effect associated with stimulant laxatives. Additionally, stimulant laxatives are associated with the possibility of nerve damage in long-term use and are the most commonly abused laxatives. Their onset in action is quicker than

HINTS AND TIPS BOX 6.6: CONSTIPATION

Administration of suppositories	1. Wash your hands 2. Lie on one side with your knees pulled up towards your chest 3. Gently push the suppository, pointed end first, into your back passage with your finger 4. Push the suppository in as far as possible 5. Lower your legs, roll over onto your stomach and remain still for a few minutes 6. If you feel your body trying to expel the suppository, try to resist this. Lie still and press your buttocks together 7. Wash your hands
Sachets containing ispaghula husk	Once the granules have been mixed with water the drink should be taken as soon as the effervescence subsides because the drink 'sets' and becomes undrinkable
Prolonged use of lactulose	In children this can contribute to the development of dental caries. Patients should be instructed to pay careful attention to dental hygiene
Lactulose taste	The sweet taste is unpalatable to many patients, especially if high doses need to be taken
Bisacodyl	Bisacodyl tablets are enterically coated and therefore patients should be told to avoid taking antacids and milk at the same time because the coating can be broken down leading to dyspepsia and gastric irritation
Laxative abuse	Some people, especially young women, use laxatives as a slimming aid. Any very slim person who is regularly purchasing laxatives should be politely asked about why they are taking the laxatives. An opening question could be phrased 'We've noticed that you have been buying quite a lot of these and we are concerned that you should be better by now, is there anything we can do for you to help?'
Onset of action	Stimulants are the quickest acting laxative, usually within 6 to 12 hours. Lactulose and bulk-forming laxatives may take 48 to 72 hours before an effect is seen
Which laxative to use in pregnancy?	Fibre supplementation and bulk-forming agents are considered to be safe and should therefore be first-line treatments wherever possible. Stimulant laxatives and macrogols also appear to be safe in pregnancy. Stimulant laxatives are more effective than bulk-forming laxatives but are more likely to cause diarrhoea and abdominal pain
Avoid drinks with caffeine	These can act as a diuretic and serve to make constipation worse
Combining laxatives	There is little evidence on the beneficial effect of combining different classes of laxatives. However, in refractory cases this approach might be justifiable

other laxative classes, with patients experiencing a bowel movement in 8 to 12 hours. They can be taken by all patient groups, have no drug interactions and are safe in pregnancy and breast-feeding. However, because of their stimulant effect on uterine contractions they are best avoided in pregnancy if possible.

Bisacodyl (Dulcolax)

Bisacodyl is available as either tablets or suppositories and can be given to patients aged over 4 years old. The dose should be taken at bedtime. For children aged between 4 and 10 years the dose is 5 mg (one tablet or one paediatric suppository) and for adults and children over 10 years the dose is 5 to 10 mg (one to two tablets or one Dulcolax 10 mg suppository).

Glycerol suppositories

Glycerol suppositories are normally used when a bowel movement is needed quickly. The patient should experience a bowel movement in 15 to 30 minutes. Varying sizes are made and can be used by all ages. The 1 g suppositories are designed for infants, the 2 g for children and the 4 g for adults.

Senna (e.g. Senokot, Nylax)

Senna is available as syrup, tablets or granules. All products deliver 7.5 mg of sennoside per dose except granules and Senokot Max, which deliver 15 mg per dose, and Ex-Lax Senna Pills (20 mg per dose) and Ex-Lax Senna (25 mg per dose). Adults and children over 12 should take 15 to 30 mg each day, preferably at bedtime. For children over 6 the dose is half that of the adult dose (7.5 to 15 mg) and for children over the age of 2 the dose is 3.75 to 7.5 mg (half to one 5 mL spoonful) each day.

Sodium picosulphate (e.g. Laxoberal liquid)

Adults and children over 10 years old should take one to two 5 mL spoonfuls (5 to 10 mg) at night. Children aged

between 4 and 10 years old can take half the adult dose (half to one 5 mL spoonful (2.5 to 5 mg)) at night. Children aged under 4 can take Laxoberal but the dose must be based on the child's weight (250 µg/kg). Sodium picosulphate is also available in a solid dose form (Dulcolax perles) for children aged over 10 years.

Osmotic laxatives (e.g. Lactulose, macrogols and magnesium salts)

These act by retaining fluid in the bowel by osmosis or by changing the pattern of water distribution in the faeces. Flatulence, abdominal pain and colic are frequently reported. They can be taken by all patient groups, have no drug interactions and can be safely used in pregnancy and breast-feeding.

Lactulose

Lactulose is given twice daily for all ages. The dose for adults is 15 mL, for children aged between 5 and 10 the dose is 10 mL, those aged between 1 and 5 the dose is 5 mL and children under 1 year is 2.5 mL. The dose for all ages can be reduced according to the need of the patient after 2 to 3 days. It has been reported that up to 20% of patients experience troublesome flatulence and cramps, although these often settle after a few days. It may take 48 hours or longer for it to work.

Macrogols (Idrolax, Movicol)

Macrogols are available as powders that are reconstituted with water. They are licensed for chronic constipation and should therefore not be routinely recommended by pharmacists because treatment should be only instigated in those presenting with acute constipation. The BNF highlights doses for the respective products.

Magnesium salts

Magnesium, when used as a laxative, is usually given as magnesium hydroxide. The adult dose ranges between 20 and 50 mL when needed. It is generally not recommended for use in children but is commonly prescribed in the elderly.

Stool softeners (liquid paraffin and docusate sodium)

Liquid paraffin has been traditionally used to treat constipation. However, the adverse side effect profile of liquid paraffin now means it should never be recommended because other, safer and more effective medications are available.

Docusate sodium

Docusate sodium is a non-ionic surfactant that has stool-softening properties that allow penetration of intestinal fluids into the faecal mass. It also has weak stimulant properties. Docusate is available as either capsules (Dioctyl, DulcoEase) or solution (Docusal). It can be given to children aged 6 months and over. Children between the age of 6 months and 2 years should take 12.5 mg (5 mL of Docusal paediatric solution) three times a day. For children aged between 2 and 12 the dose is 12.5 to 25 mg (5 to 10 mL) three times a day. Adults and children over 12 years old should take up to 500 mg daily in divided doses. In contrast to liquid paraffin, docusate sodium seems to be almost free of any side effects. Docusate sodium can be given to all patients.

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Web sites

Prodigy guidance: http://cks.library.nhs.uk/constipation

Irritable bowel syndrome

Background

Irritable bowel syndrome (IBS) is one of the commonest GI tract conditions seen in primary care. Approximately 25% of GP consultations for GI conditions are finally diagnosed as IBS. It can be defined as a functional bowel

disorder (i.e. absence of abnormality) in which abdominal pain and bloating is associated with a change in bowel habit. The diagnosis is suggested by the presence of long-standing colonic symptoms without any deterioration in the patient's general condition. Diagnostic criteria (e.g. Rome II criteria) have been developed to define IBS but these are little used in a clinical setting and are more applicable for research purposes.

Prevalence and epidemiology

IBS is common. Adult prevalence rates in Western countries are reported to be between 10 and 15%, with approximately twice as many women than men affected. It most commonly affects people between 20 and 30 years old but recent trends indicate that there is a significant prevalence of IBS in older people.

Aetiology

No anatomic cause can be found to explain the aetiology of IBS but it is now clearly understood to be multifactorial. Many factors can contribute to disease expression and include motility dysfunction, diet and genetics. In a small proportion of cases symptoms appear after bacterial gastroenteritis. Psychological factors also influence symptom reporting and consultation and some studies have shown patients who suffer from higher levels of stress or depression experience worse symptoms when compared to other patients. Flare-up of symptoms has also been associated with periods of increased stress. Symptoms of diarrhoea and constipation appear to be linked with hyperactivity of the small intestine and colon in response to food ingestion and parasympathomimetic drugs. Excessive parasympathomimetic activity might account for mucus associated with the stool.

Arriving at a differential diagnosis

As only 20 to 30% of people with IBS symptoms consult their doctor the pharmacist has a pivotal role to play in establishing a diagnosis. A diagnosis of IBS relies almost exclusively on taking a thorough history as physical examination and diagnostic tests such as rectal examination and biopsy are of limited use. A number of IBS-specific questions should always be asked of the patient to aid in diagnosis (Table 6.16).

Clinical features of IBS

IBS is characterised by abdominal pain or discomfort, located especially in the left lower quadrant of the abdomen, which is sometimes relieved by defecation or the passage of wind. Altered defecation, either constipation or diarrhoea, with associated bloating is also normally present. People with IBS can present with 'diarrhoea-predominant', 'constipation-predominant' or alternating symptom profiles. During bouts of diarrhoea,

Table 6.16
Specific questions to ask the patient: IBS

Question	Relevance
Age	• IBS usually affects people under the age of 45 • Particular care is required in labelling middle-aged (over 45 to 50 years old) and elderly patients with IBS when presenting with bowel symptoms for the first time. Such patients are best referred for further evaluation to eliminate organic bowel disease
Periodicity	• IBS tends to be episodic. The patient might have a history of being well for a number of weeks or months in between bouts of symptoms. Often patients can trace their symptoms back many years, even to childhood
Presence of abdominal pain	• The nature of pain experienced by patients with IBS is very varied, ranging from localised and sharp to diffuse and aching. It is therefore not very discriminatory; however, the patient will probably have experienced similar abdominal pain in the past. Any change in the nature and severity of the pain is best referred for further evaluation
Location of pain	• Pain from IBS is normally located in the left lower quadrant. For further information on other conditions that cause pain in the lower abdomen see pages 171–172
Diarrhoea and constipation	• Patients with IBS experience altered defecation. They do not have textbook definitions of constipation or diarrhoea but bowel function will be different from normal • Constipation-predominant IBS is more common in women • The presence of blood in the stool is not usual in IBS and can suggest inflammatory bowel disease

mucus tends to be visible on the stools. Patients might also complain of increased stool frequency but pass normal or pellet-like stools. Diarrhoea on wakening and shortly after meals is also observed in many patients. Patients will normally have a long-standing history of symptoms (NICE Guidance, August 2007 states primary care clinicians should consider assessment for IBS if the patient reports having had change in bowel habit, abdominal pain/discomfort or bloating for at least 6 months).

Conditions to eliminate

Constipation and diarrhoea

As the major presenting symptom of IBS is an alteration in defecation, it is necessary to differentiate IBS from acute and chronic causes of constipation and diarrhoea. For further information on differentiating these conditions from IBS please refer to page 149 (for constipation) and page 143 (for diarrhoea).

Figure 6.13 will aid differentiation of IBS from other abdominal conditions.

TRIGGER POINTS indicative of referral: Irritable bowel syndrome

- Blood in the stool
- Children under 16
- Fever
- Nausea and/or vomiting
- Patients over 45 with recent change to bowel habit
- Patients with no previous history of IBS and no precipitating factors
- Severe abdominal pain
- Steatorrhoea

Evidence base for over-the-counter medication

Before medicines are recommended it might be useful to discuss if stress is a factor and if this can be avoided. In addition, dietary modification has shown to be effective

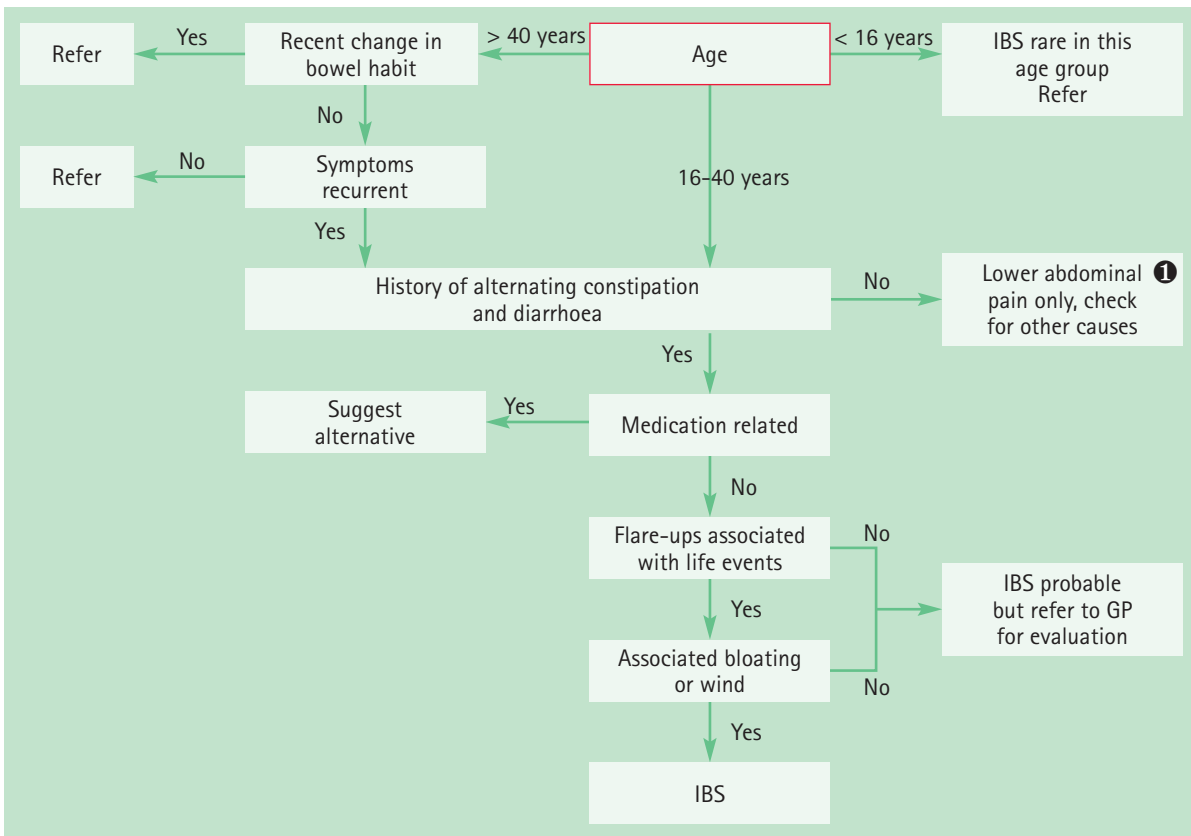

Fig. 6.13 Primer for differential diagnosis of irritable bowel syndrome

❶ **Lower abdominal pain**
See Fig. 6.29 for primer for differential diagnosis of abdominal pain.

for some patients. Suspected food products must be excluded from the diet for a minimum of 2 weeks and then gradually reintroduced to determine if the food item triggers symptoms.

Medicines are generally needed but those with a specific licence for IBS have a poor evidence base. These include mebeverine, alverine, hyoscine and peppermint oil and are generally used to treat abdominal pain and discomfort. In addition, bulk-forming and stimulant laxatives can be used to treat constipation-predominant IBS and loperamide for diarrhoea-predominant IBS. Both laxatives and diarrhoeals can be taken on a regular basis using the lowest effective dose. The following text only concentrates on the evidence for those products specifically marketed for the treatment of IBS.

Hyoscine

A number of trials have investigated the effectiveness of hyoscine in the treatment of IBS. However, only three trials of sufficient methodological quality allow conclusions to be drawn regarding its effectiveness. Each of the three trials demonstrated partial symptomatic improvement in some of the patients, although no trial proved hyoscine to be significantly better than placebo. A recent meta-analysis conducted by Poynard et al (2001) confirmed these findings and suggested that hyoscine was the least effective of the six smooth muscle relaxant medicines reviewed.

Antispasmodics (mebeverine, alverine and peppermint oil)

Mebeverine has been available as a POM for many years and as a pharmacy medicine since 1996, yet trial data to support its effectiveness are mixed. Conclusions drawn from five well-designed trials (two published in non-English) are conflicting. Of the three papers written in English, two studies appear to show a significant effect and one no effect. The meta-analysis by Poynard et al suggests a significant difference exists between mebeverine and placebo when data from all trials (including the two non-English trials) are combined.

Even fewer trials appear to have been conducted with alverine than mebeverine. One study by Tudor (1986) compared alverine to mebeverine in 45 patients; the authors concluded that alverine had similar efficacy to mebeverine. However, no placebo group was included in this study and it is therefore unclear to what extent alverine is effective.

Peppermint oil is the major constituent of several OTC remedies yet it has little evidence to support its effectiveness. Pittler & Ernst (1998) evaluated eight randomised controlled trials involving peppermint oil. Collectively, they indicate that peppermint oil could be efficacious for symptom relief in IBS but study design limitations meant that definitive judgement about efficacy was not possible.

Summary

A recent Cochrane review by Quartero et al (2005) concluded that antispasmodics were beneficial for abdominal pain and global assessment scores but it could not be shown whether antispasmodic subgroups were individually effective. It must also be noted that the majority of trials in this review were for products not available OTC. Based on the available evidence for OTC products, mebeverine should be first-line choice.

Alternative treatments

Herbal remedies for IBS have been subject to a Cochrane review (Liu et al 2006). Seventy-five trials were reviewed involving 71 different herbal medicines, although most trials were deemed to be of poor methodological quality. Nonetheless, the review concluded that certain remedies, in particular STW5, Padma Lax and Tongxie Yaofang, improved IBS symptoms.

Practical prescribing and product selection

Prescribing information relating to the medicines used for IBS reviewed in the section 'Evidence base for over-the-counter medication' is discussed and summarised in Table 6.17; useful tips relating to the treatment of patients with IBS are given in Hints and Tips Box 6.7.

All marketed products can be given to children (see individual entries) but anyone aged under 16 suspected of having IBS for the first time should be referred to a GP.

Hyoscine butylbromide (Buscopan IBS Relief)

The recommended starting dose for adults is one tablet three times a day, although this can be increased to two tablets four times a day if necessary. It is not recommended for children under the age of 12. It is a quaternary derivative of hyoscine so it does not readily cross the blood–brain barrier and therefore sedation is not normally encountered, although it might cause dry mouth and constipation. Because of its anticholinergic effects it is best avoided with other medicines that also have anticholinergic effects, for example, antihistamines, tricyclic antidepressants, neuroleptics and disopyramide. It can be given during pregnancy and breast-feeding but should be avoided if possible. It should also be avoided in patients with glaucoma, myasthenia gravis and prostate enlargement.

Mebeverine (Colofac IBS)

Adults and children 10 years and over should take one tablet three times a day, preferably 20 minutes before meals. Mebeverine is not known to interact with other medicines, has no cautions in its use and can be given in pregnancy and breast-feeding although there is a lack

Table 6.17
Practical prescribing: Summary of IBS medicines

Name of medicine	Use in children	Likely side effects	Drug interactions of note	Patients in whom care should be exercised	Pregnancy and breast-feeding
Hyoscine (Buscopan)	>12 years	Constipation and dry mouth	Tricyclic antidepressants, neuroleptics, antihistamines and disopyramide	Glaucoma, myasthenia gravis and prostate enlargement	Avoid if possible
Mebeverine Colofac IBS	>10 years	None	None	None	OK
Peppermint oil Colpermin	>15 years	Heartburn	None	None	OK in pregnancy; try to avoid in breast-feeding
Mintec	>18 years				
Equilon herbal	Not recommended				
Alverine	>12 years	Rash	None	None	OK

HINTS AND TIPS BOX 6.7: IRRITABLE BOWEL SYNDROME

Non-drug treatment	Hypnotherapy has been reported as being effective for some patients. A register of IBS therapists specialising in hypnotherapy can be found at http://www.ibs-register.co.uk

of detailed studies. It is associated with very few side effects, although allergic reactions have been reported.

Alverine (Spasmonal)

Adults and children over 12 years should take one or two capsules three times a day before food. Like mebeverine, it is not known to interact with other medicines, has no cautions in its use and can be given in pregnancy and breast-feeding, although there is a lack of detailed studies. It has no interactions with other medicines and can be used by all patient groups. It can cause nausea, headache, dizziness, itching, rash and allergic reactions.

Peppermint oil (e.g. Mintec, Colpermin, Equilon herbal)

Adults and children aged over 15 years can take peppermint oil. The dose is one capsule three times a day before food, which can be increased to two capsules three times a day in severe symptoms. It often causes heartburn and rarely allergic rashes have been reported. It is safe to use in pregnancy but can decrease breast milk production. It has no drug interactions and can be used by all patient groups.

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Web sites

IBS Self-help groups and associations: http://www.ibsgroup.org, http://www.ibsnetwork.org.uk and http://www.ibsassociation.org/
Articles: Thomas L. Current management options for irritable bowel syndrome. Available at http://www.escriber.com/Prescriber/Features.asp?ID=1042&GroupID=6&Action=View
Prodigy guidance: http://cks.library.nhs.uk/irritable_bowel_syndrome
NICE guidelines (draft): http://www.nice.org.uk/page.aspx?o=291060 (accessed 30 Nov 2007).

Haemorrhoids

Background

Haemorrhoids (piles) are the most common problem affecting the anorectal region. Patients might feel embarrassed talking about symptoms and it is therefore important that any requests for advice are treated sympathetically and away from others to avoid embarrassment.

Prevalence and epidemiology

The exact prevalence of haemorrhoids is unknown but it is estimated that one in two people will experience at least one episode at some point during their lives. Haemorrhoids can occur at any age but are rare in children and adults under the age of 20. It affects both sexes equally and is more common with increasing age, especially in people aged between 40 and 65 years of age. There is a high incidence of haemorrhoids in pregnant women.

Aetiology

The cause of haemorrhoids is probably multifactorial with anatomical (degeneration of elastic), physiological (increased anal canal pressure) and mechanical (straining at stool) processes implicated. Haemorrhoids have been traditionally described as engorged veins of the haemorrhoidal plexus. The analogy of varicose veins of the anal canal is often used but is misleading. Current thinking favours the theory of prolapsed anal cushions. Anal cushions maintain fine continence and are submucosal vascular structures suspended in the canal by a connective tissue framework derived from the internal anal sphincter and longitudinal muscle. Within each of the three cushions is a venous plexus that is fed by arteriovenous blood supply. Veins in these cushions fill with blood when sphincters inside them relax and empty when the sphincters contract. Fragmentation of the connective tissue supporting the cushions leads to their descent and is due to anatomical, physiological and mechanical processes. The prolapsed anal cushion has impaired venous return resulting in venous stasis and inflammation of the cushion's epithelium.

Haemorrhoids are classified as either internal or external. This distinction is an anatomical one. Superior to the anal sphincter there is an area known as the dentate line. At this junction epithelial cells change from squamous to columnar epithelial tissue. Above the dentate line haemorrhoids are classed as internal and below, external. Furthermore internal haemorrhoids are graded according to severity: grade I – do not prolapse out of the anal canal; grade II – prolapse on defecation but reduce spontaneously; grade III – require manual reduction; and grade IV – cannot be reduced.

Arriving at a differential diagnosis

In the first instance most patients with anorectal symptoms will self-diagnose haemorrhoids and often self-treat due to embarrassment about symptoms. Requests for advice need to be treated sympathetically, away from others, and importantly this gives the pharmacist the opportunity to confirm the patient's self diagnosis. Bleeding tends to cause the greatest concern and often instigates the patient to seek help. Invariably, rectal bleeding is of little consequence but should be thoroughly investigated to exclude sinister pathology. A number of haemorrhoid-specific questions should always be asked (Table 6.18).

Clinical features of haemorrhoids

Symptoms experienced by the patient are dependent upon the severity or type of haemorrhoid and can include bleeding, perianal itching, mucus discharge and pain. Often patients are asymptomatic until the haemorrhoid prolapses. Any blood associated is bright red and is most commonly seen as spotting around the toilet pan, streaking on toilet tissue or visible on the surface of the stool. Symptoms are often intermittent and each episode usually lasts from a few days to a few weeks

Internal haemorrhoids are rarely painful whereas external haemorrhoids often cause pain due to the

Table 6.18
Specific questions to ask the patient: Haemorrhoids

Question	Relevance
Duration	• Patients with haemorrhoids tend to have had symptoms for some time before requesting advice. However, patients with symptoms that have been present for more 3 weeks should be referred
Pain	• Pain associated with haemorrhoids tends to occur on defecation and at times other than defecation, for example, when sitting. It is usually described as a dull ache • Sharp or stabbing pain at the time of defecation can suggest an anal fissure or tear
Rectal bleeding	• Slight rectal bleeding is often associated with haemorrhoids. Blood appears bright red and might be visible in the toilet bowl or on the surface of the stool. The presence of blood is usually a direct referral sign but if the cause is haemorrhoids this could be treated unless the patient is unduly anxious in which case referral is appropriate • Blood mixed in the stool has to be referred to eliminate a GI bleed • Large volumes of blood or blood loss not associated with defecation must be referred to eliminate possible carcinoma
Associated symptoms	• Symptoms associated with haemorrhoids are usually localised, for example, anal itching. Other symptoms such as nausea, vomiting, loss of appetite and altered bowel habit should be viewed with caution and underlying pathology suspected. Referral would be needed
Diet	• A lack of dietary fibre that leads to constipation is a contributory factor to haemorrhoids. The passage of hard stools and straining during defecation can cause haemorrhoids. Find out about the patient's diet and current bowel habits

cushion becoming thrombosed. Pain is described as a dull ache that increases in severity when the patient defecates leading to patients ignoring the urge to defecate. This can then lead to constipation, which in turn will lead to more difficulty in passing stools and further increase the pain associated with defecation.

Conditions to eliminate

Dermatitis

Localised anal itching can result from dermatitis (or even threadworm infection). If pruritus is the only presenting symptom then the most likely cause is contact dermatitis caused by toiletries.

Medication

As constipation is a contributory factor in the manifestation of haemorrhoids, those medicines that are prone to causing constipation should, if possible, be avoided. Table 6.14 lists those medicines that are commonly known to cause constipation.

Conditions causing rectal bleeding

A number of conditions can present with varying degrees of rectal bleeding. However, other symptoms should be present that will allow them to be excluded.

Anal fissure

Anal fissures are common, with the 20- to 30-year-old age group most affected. Symptoms often follow a period of constipation and are normally caused by straining at stool. Pain can be intense on defecation and can last between a few minutes and a few hours after defecation. Bright red blood is commonly seen. Non-urgent referral is necessary for confirmation of the diagnosis. In the meantime the patient should be instructed to eat more fibre and increase their fluid intake.

Ulcerative colitis and Crohn's disease

Other symptoms besides blood in the stool are usually present with ulcerative colitis and Crohn's disease. These tend to be stools that are watery, abdominal pain in the lower left quadrant, weight loss and fever. Patients will appear unwell and also find that they have urgency, nocturnal diarrhoea and early morning rushes. In the acute phase patients will have malaise.

Upper GI bleeds

Erosion of the stomach wall or upper intestine is normally responsible for GI bleeds and is often associated with NSAID intake. The colour of the stool is related to the rate of bleeding. Stools from GI bleeds can be tarry (indicating a bleed of 100 to 200 mL of blood) or black (indicating a bleed of 400 to 500 mL of blood). Urgent referral is needed.

Colorectal cancer

Rectal carcinoma is most common in the 50- to 70-year-old age group and is characterised by rectal bleeding, a change in bowel habit and tenesmus. Rectal bleeding tends to be persistent and steady though slight for all tumours. Colorectal bleeds depend on the site of tumour, for example, sigmoid tumours lead to bright red blood in or around the stool. Any middle-aged patient presenting with rectal bleeding and a change of bowel habit must be referred. NICE have produced referral guidelines for doctors for suspected cases of colorectal cancer (http://www.nice.org.uk/guidance/CG27).

Figure 6.14 will aid the differentiation of haemorrhoids.

TRIGGER POINTS indicative of referral: Haemorrhoids

- Abdominal pain
- Blood mixed in the stool
- Fever
- Patients who have to reduce their haemorrhoids manually
- Persistent change in bowel habit in middle-aged patients
- Severe pain associated with defecation
- Unexplained rectal bleeding

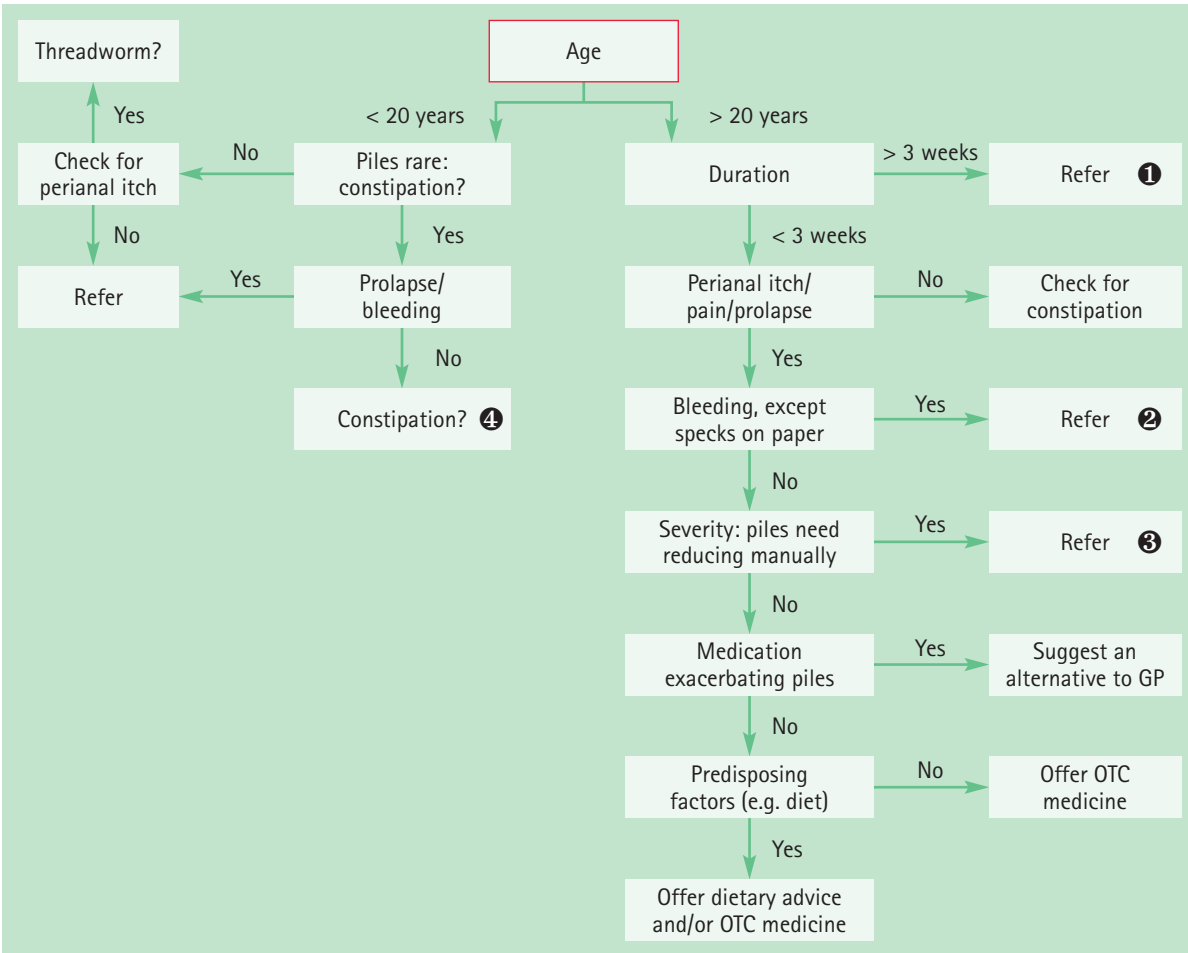

Fig. 6.14 Primer for differential diagnosis of haemorrhoids

❶ Duration
Patients with long-standing symptoms that have not been seen previously by the GP should be referred to eliminate any underlying pathology. In the vast majority of cases no sinister findings will result.

❷ Rectal bleeding
In the majority of cases rectal bleeding is a sign of referral. However, in cases where sinister pathology has been excluded and only mild local bleeding has occurred the pharmacist could instigate treatment.

❸ Severity
Medication is unlikely to help any patient who has to manually reduce haemorrhoids. Referral for other treatments is recommended.

❹ Constipation
See Fig. 6.12.

Evidence base for over-the-counter medication

Diet

Reviews by Alonso-Coelle et al (2005, 2006) have concluded that general measures to prevent constipation will help to decrease straining during defecation, ease the symptoms of haemorrhoids and reduce recurrence. Patients should therefore be asked about their normal diet to determine fibre intake. Those with diets low in fibre should be encouraged to increase their fibre and fluid intake; this will help produce softer stools and reduce constipation. Patients should try to eat more fruit, vegetables, bran and wholemeal bread. If this is not possible then fibre supplementation with a bulk-forming laxative could be recommended. Bulk-forming laxatives will take 2–3 days to relieve constipation and may take up to 6 weeks to improve symptoms of haemorrhoids.

Pharmacological intervention

Numerous products are marketed for the relief and treatment of haemorrhoids. These include a wide range of therapeutic agents and commonly include anaesthetics, astringents, anti-inflammatories and protectorants. Most products contain a combination of these agents with some having three or more different agents included.

The inclusion of such a diverse range of chemical entities appears to be based largely on theoretical grounds rather than any evidence base. Extensive literature searching found only one published trial regarding the efficacy of any marketed product (Ledward 1980); however, this trial suffered from serious methodological flaws.

Anaesthetics (lidocaine, benzocaine and cinchocaine)

No trials appear to have been conducted using local anaesthetics in the treatment and relief of symptoms for haemorrhoids. However, anaesthetics have proven efficacy when used on other mucosal surfaces; their use could therefore be justifiably recommended. Their action is short-lived and will produce temporary relief from perianal itching and pain. They require frequent application and might therefore cause skin sensitisation.

Astringents (allantoin, bismuth, zinc, Peru balsam)

Astringents are included in haemorrhoid preparations on the theoretical basis that they precipitate surface proteins thus producing a protective coat over the haemorrhoid. There appears to be no evidence to support this theory. Certain proprietary products only contain astringents and at best will provide a placebo effect.

Anti-inflammatories (hydrocortisone)

Steroids have proven effectiveness in reducing inflammation and would therefore be useful in reducing haemorrhoidal swelling. Trials with OTC products containing hydrocortisone appear not to have taken place. It must be assumed that manufacturers have incorporated hydrocortisone into haemorrhoid products on the assumption that they will have an effect. Recommendation of a steroid-containing product is probably justified.

Protectorants (e.g. shark liver oil)

Protectorants are claimed to provide a protective coating over the skin and thus produce temporary relief from pain and perianal itch. These claims cannot be substantiated and, as with astringents, any benefit conveyed by a protectorant is probably a placebo effect. In addition, there is also an ethical dimension to using a product with no efficacy sourced from sharks.

Other agents

Sclerosing agents (lauromacrogol) and wound-healing agents (yeast cell extract) can also be found in some products. There is no evidence supporting their effectiveness.

Flavanoids

Dietary supplementation with flavanoids is a common alternative treatment that is popular in continental Europe and the Far East. As an adjunct, their use has been shown to reduce acute symptoms and secondary haemorrhage after haemorrhoidectomy.

Summary

With so little data available on their effectiveness it is impossible to say whether any product is a credible treatment for haemorrhoids, and many medical authorities regard them as little more than placebos. However, products containing a local anaesthetic or hydrocortisone will probably confer some benefit, and they do have proven effectiveness in other similar conditions. It would therefore seem most prudent if recommending a product that it should contain one or both of these chemical entities.

Treatment should only be recommended to patients with mild haemorrhoids. Any person complaining of prolapsing haemorrhoids, which need reducing by the patient, should be referred because these patients require non-surgical intervention with sclerotherapy or rubber band ligation. If these fail to cure the problem then a haemorrhoidectomy might be performed.

Practical prescribing and product selection

Prescribing information relating to the medicines used for haemorrhoids reviewed in the section 'Evidence base for over-the-counter medication' is discussed and summarised in Table 6.19.

Table 6.19
Practical prescribing: Summary of haemorrhoid products

	Form	Anaesthetics	Astringents	Steroids	Protectorant
Anacal*	Cream or suppository	No	No	No	No
Anodesyn	Ointment or suppository	Yes	Yes	No	No
Anusol	Cream, ointment or suppository	No	Yes	No	No
Anusol Plus HC	Ointment or suppository	No	Yes	Yes	No
Germoloids	Cream, ointment or suppository	Yes	Yes	No	No
Germoloids HC	Spray	Yes	No	Yes	No
Hemocane	Cream	Yes	No	No	No
Nupercainal	Ointment	Yes	No	No	No
Perinal	Spray	Yes	No	Yes	No
Preparation H**	Ointment or suppository	No	No	No	Yes
Preparation H	Gel	No	Yes	No	No

*Contains a sclerosing agent
**Contains yeast cell extract

The product licences of products for haemorrhoids allow all patient groups, except children under 12 years, to use them. (Note – good practice dictates that people under 20 years old with suspected haemorrhoids should be referred.) They do not interact with any other medicines and can be used in pregnancy. The standard dose for any formulation is twice daily, plus application after each bowel movement. Minimal side effects have been reported and are usually limited to slight irritation. Products that contain hydrocortisone are subject to several licensing restrictions: they are restricted to use in patients over a certain age (Perinal spray 14 years, Germoloids spray 16 years and Anusol Plus products 18 years); they should be used for no longer than a week's duration; and they should not be used by pregnant or lactating women.

Further reading

Alonso-Coello P, Guyatt G, Heels-Ansdell D, et al. Laxatives for the treatment of hemorrhoids. The Cochrane Database of Systematic Reviews 2005, issue 4.
Alonso-Coello P, Mills E, Heels-Ansdell D, et al. Fiber for the treatment of hemorrhoids complications: a systematic review and meta-analysis. Am J Gastroenterol 2006;101:181–8.
Alonso-Coello P, Zhou Q, Martinez-Zapata MJ, et al. Meta-analysis of flavonoids for the treatment of haemorrhoids. Br J Surg 2006;93:909–20.
Nisar PJ, Scholefield JH. Managing haemorrhoids. Br Med J 2003:327;847–51.
Ledward RS. The management of puerperal haemorrhoids: A double blind clinical trial of Anacal rectal ointment. Practitioner 1980;224:660–1.

Web sites

Prodigy guidance: http://cks.library.nhs.uk/haemorrhoids
Chemist and Druggist: http://www.dotpharmacy.com/upmain.html (August 2006 update).

Abdominal pain

Background

Abdominal pain is a symptom of many different conditions, ranging from acute self-limiting problems to life-threatening conditions such as ruptured appendicitis and bowel obstruction. However, the overwhelming majority of cases will be of a non-serious nature, self-limiting and not require medical referral. The most common conditions that present to community pharmacies are dyspepsia affecting the upper abdomen and IBS affecting the lower abdomen. These are covered in more detail on pages 167 and 170. However, other conditions will present with abdominal pain (Fig. 6.15 and Table 6.20) and these are covered in this chapter.

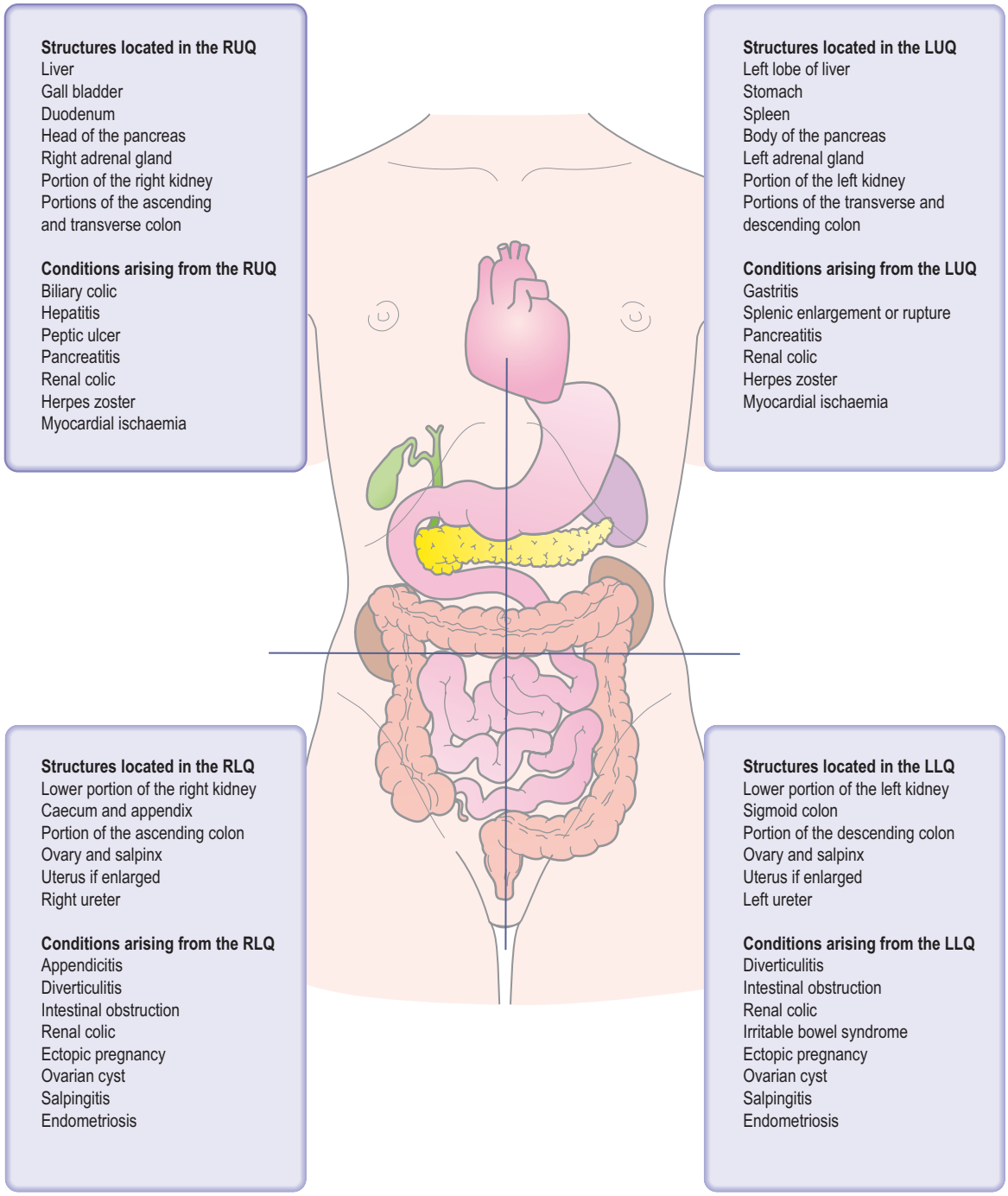

Fig. 6.15 Anatomical location of organs and conditions that can cause abdominal pain

Prevalence and epidemiology

The prevalence and epidemiology of abdominal pain within the population is determined by those conditions that cause it. As so many conditions can give rise to abdominal pain it is likely that the majority of the population will, at some point, suffer from abdominal pain. For example, one study found that 40% of the UK population had suffered from dyspepsia during the previous 12 months and gastroenteritis, which is commonly associated with abdominal pain, is extremely common.

Aetiology

Abdominal pain does not only arise from the GI tract but also from the cardiovascular and musculoskeletal system. Therefore, the aetiology of abdominal pain is dependent on its cause. For example, GI tract causes include poor

Table 6.20
Causes of abdominal pain

Probability	Cause		
	Upper abdomen	**Lower abdomen**	**Diffuse**
Most likely	Dyspepsia	Irritable bowel syndrome	Gastroenteritis
Likely	Peptic ulcers	Diverticulitis (elderly)	Not applicable
Unlikely	Cholecystitis, cholelithiasis, renal colic	Appendicitis, endometriosis, renal colic	Not applicable
Very unlikely	Splenic enlargement, hepatitis, myocardial infarction	Ectopic pregnancy, salpingitis, intestinal obstruction	Pancreatitis, peritonitis

Table 6.21
Specific questions to ask the patient: Abdominal pain

Question	Relevance
Location of pain	• Knowing the anatomical location of abdominal structures is helpful in the differential diagnosis of abdominal pain (Fig. 6.15)
Presence only of abdominal pain/ discomfort	• In general, patients without other symptoms rarely have serious pathology. The symptoms are usually self-limiting and often no cause can be determined
Nature of the pain	• Heartburn is classically associated with a retrosternal burning sensation • Cramp-like pain is seen in diverticulitis, IBS, salpingitis and gastroenteritis • Colicky pain (pain that comes and goes) has been used to describe the pain of appendicitis, biliary and renal colic and intestinal obstruction • Gnawing pain is associated with pancreatitis and pancreatic cancer, and boring pain with ulceration
Radiating pain	• Abdominal pain that moves from its original site should be viewed with caution • Pain that radiates to the jaw, face and arm could be cardiovascular in origin • Pain that moves from a central location to the right lower quadrant could suggest appendicitis • Pain radiating to the back may suggest peptic ulcer or pancreatitis
Severity of pain	• Non-serious causes of abdominal pain generally do not give rise to severe pain. Pain associated with pancreatitis, biliary and renal colic and peritonitis tends to be severe (subjective scores higher than 6 out of 10)
Age of patient	• With increasing age, abdominal pain is more likely to have an identifiable and serious organic cause. Appendicitis is the only serious abdominal condition that is much more common in young patients
Onset & duration	• Onset can be gradual or sudden. In general, if no identifiable cause can be found, abdominal pain with sudden onset is generally a symptom of more serious conditions. For example, peritonitis, appendicitis, ectopic pregnancy, renal and biliary colic • Pain that lasts more than 6 hours is suggestive of underlying pathology
Aggravating or ameliorating factors	• The presence of food can aggravate gastric ulcers and antacids can relieve symptoms • Biliary colic can be aggravated by fatty foods • Vomiting tends to relieve pain in gastric ulcers • Pain in duodenal ulcer is relieved after ingestion of food • Pain in salpingitis, pancreatitis and appendicitis is often made worse by movement
Associated symptoms	• Vomiting, weight loss, melaena, altered bowel habit and haematemesis are all symptoms that suggest more serious pathology and require referral

muscle tone leading to reflux (e.g. lower oesophageal sphincter incompetence), infections that cause peptic ulcers (from *H. pylori*) and mechanical blockages causing renal and biliary colic. Cardiovascular causes include angina and myocardial infarction whereas musculoskeletal problems often involve tearing of abdominal muscles.

Arriving at a differential diagnosis

The main role of the community pharmacist is to identify patients in whom symptoms suggest more serious pathology, so that they can be further evaluated. This is not easy, as many abdominal conditions do not present with classical textbook symptoms in a primary care setting. Patients tend to present to the pharmacist early in the course of the disease, often before the presenting symptoms have assumed the more usual description. The low prevalence of serious disease and overlapping symptoms with minor illness makes the task even more difficult. Single symptoms are poor predictors of final diagnosis (except for reflux oesophagitis, in which the presence of heartburn is highly suggestive). It is therefore important to look for 'symptom clusters' and to use knowledge of the incidence and prevalence of conditions to determine if referral is needed. This necessitates taking a very careful history and not relying on a single symptom to label a patient with a particular problem. Specific questions relating to abdominal pain should be asked (Table 6.21).

Conditions affecting the upper abdomen

Left upper quadrant pain

Dyspepsia/gastritis

Patients with dyspepsia present with a range of symptoms that commonly involve vague abdominal discomfort (aching) above the umbilicus (Fig. 6.16) associated with belching, bloating, flatulence, feeling of fullness and heartburn. It is normally relieved by antacids and aggravated by spicy foods or excessive caffeine. Vomiting is unusual. For further information on dyspepsia see page 135.

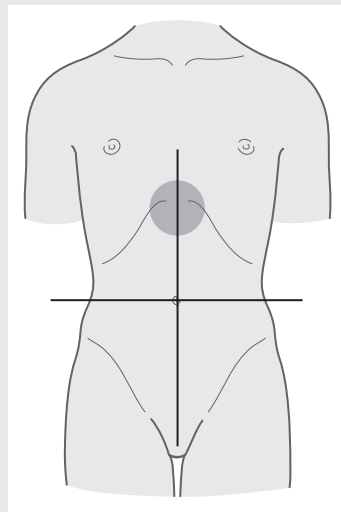

Fig. 6.16 The position of pain in gastritis and dyspepsia

Splenic enlargement or rupture

If the spleen is enlarged, generalised left upper quadrant pain associated with abdominal fullness and early feeding satiety is observed (Fig. 6.17). The condition is rare and is nearly always secondary to another primary cause, which might be an infection, a result of inflammation or haematological in origin.

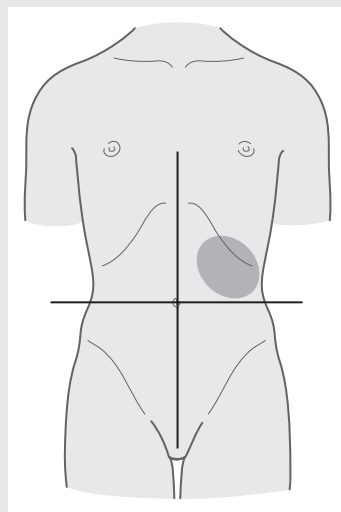

Fig. 6.17 The position of pain associated with splenic enlargement

Right upper quadrant pain

Acute cholecystitis and cholelithiasis

Acute cholecystitis (inflammation of the gall bladder) and cholelithiasis (presence of gall stones in the bile ducts, also called biliary colic) are characterised by persistent, steady severe pain (Fig. 6.18). Classically, the onset is sudden and starts a few hours after a meal, frequently waking the patient in the early hours of the morning. The pain can also be felt in the epigastric area and radiates to the tip of the right scapula in cholelithiasis. Fatty foods often aggravate the pain. The incidence increases with increasing age and is most common in people aged over 50. It is also more prevalent in women than men.

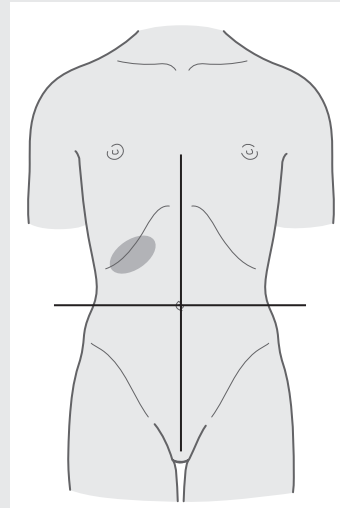

Fig. 6.18 The position of pain associated with acute cholecystitis and cholelithiasis

Hepatitis

Liver enlargement from any type of hepatitis will cause discomfort or dull pain (Fig. 6.19). Associated symptoms of general malaise, nausea, vomiting, jaundice and pruritus should be present. The most common causes of acute hepatitis are alcohol abuse and viral infection.

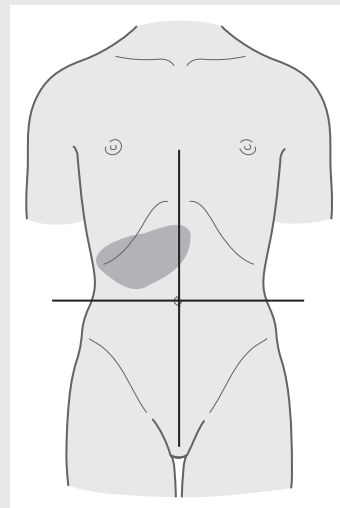

Fig. 6.19 The position of pain associated with hepatitis

Ulcers

Ulcers are classed as either gastric or duodenal. They occur most commonly in patients aged 30 to 50 years and are more common in men than women. Symptoms are variable but typically the patient will have localised mid-epigastric pain (Fig. 6.20) described as 'constant', 'annoying' or 'gnawing/boring'.

With gastric ulcers, symptoms are inconsistent but the pain usually comes on whenever the stomach is empty – usually 15 to 30 minutes after eating – and is generally relieved by antacids or food and aggravated by alcohol and caffeine. NSAID use is associated with a three- to four-fold increase in gastric ulcers.

Duodenal ulcers tend to be more consistent in symptom presentation. Pain occurs 2 to 3 hours after eating and pain that wakes a person at night is highly suggestive of duodenal ulcer.

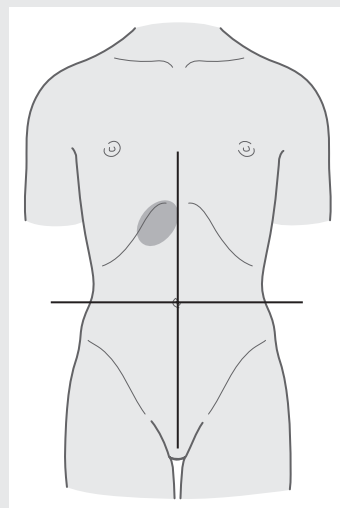

Fig. 6.20 The position of pain associated with ulcers

Pain affecting both right and left upper quadrants

Acute pancreatitis

Pain of pancreatitis develops suddenly and is described as agonising with the pain being centrally located that often radiates into the back (Fig. 6.21). Pain reaches its maximum intensity within minutes and can last hours or days. Vomiting is common but does not relieve the pain. Early in the attack patients might get relief from the pain by sitting forwards. It is commonly seen in alcoholics and it is likely that the patient will have a history of long-term heavy drinking. Patients are very unlikely to present in a community pharmacy due to the severity of the pain but a mild attack could present with steady epigastric pain sometimes centred close to the umbilicus and can be difficult to distinguish from other causes of upper quadrant pain.

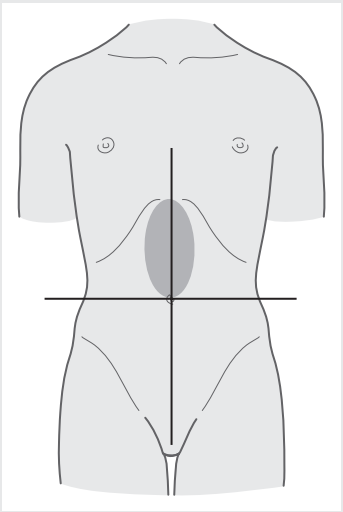

Fig. 6.21 The position of pain associated with pancreatitis

Renal colic

Urinary calculi (stones) can occur anywhere in the urinary tract, although most frequently stones get lodged in the ureter. Pain begins in the loin, radiating round the flank into the groin and sometimes down the inner side of the thigh (Fig. 6.22). Pain is severe and colicky in nature. Attacks tend to last minutes to hours and often leave the person prostrate with pain. Symptoms of nausea and vomiting might also be present. Men aged between 20 and 40 years are most likely to suffer from renal colic.

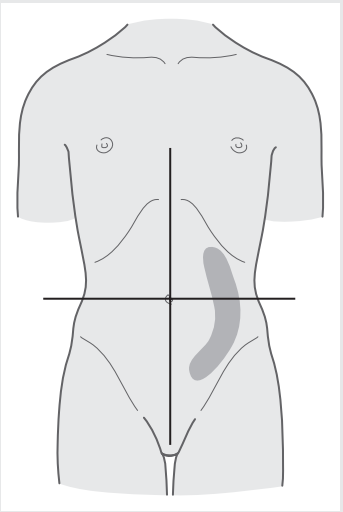

Fig. 6.22 The position of pain in renal colic

Myocardial ischaemia

Angina and myocardial infarction (MI) cause chest pain that can be difficult to distinguish initially from epigastric/retrosternal pain caused by dyspepsia (Fig. 6.23). However, pain of cardiovascular origin often radiates to the neck, jaw and inner aspect of the left arm. Typically, angina pain is precipitated by exertion and subsides after a few minutes once at rest. Pain associated with MI will present with characteristic deep crushing pain. The patient will appear pale, display weakness and be tachycardic. Cardiovascular pain should respond to sublingual glyceryl trinitrate therapy.

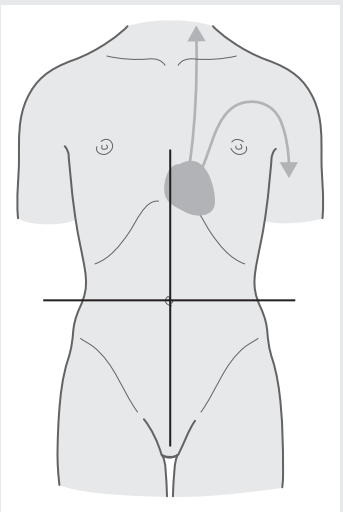

Fig. 6.23 The position of pain associated with myocardial ischaemia

Herpes zoster (shingles)

Pain associated with herpes zoster typically occurs once the rash has erupted, although it can precede the rash by several days. Pain that precedes the rash and is right-sided can be confused with appendicitis (Fig. 6.24).

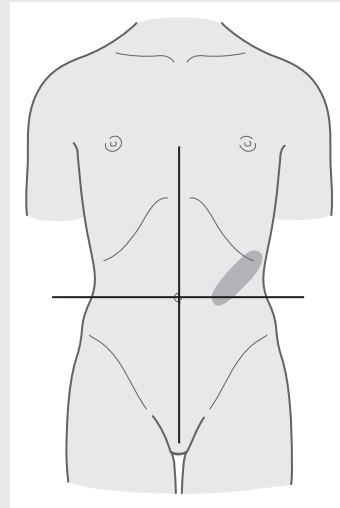

Fig. 6.24 The position of pain in herpes zoster

Conditions affecting the lower abdomen

The most common causes of lower abdominal pain are muscle strains, IBS, appendicitis and salpingitis in women. Apart from appendicitis, all these conditions can present in either quadrant.

Irritable bowel syndrome

Pain is most often observed in the left lower quadrant (Fig. 6.25); however, the discomfort can be vague and diffuse and about one-third of patients exhibit upper abdominal pain. The pain is described as 'cramp-like' and is recurrent. Alternating diarrhoea and constipation and mucus coating the stools is also often present. For further information on IBS see page 155.

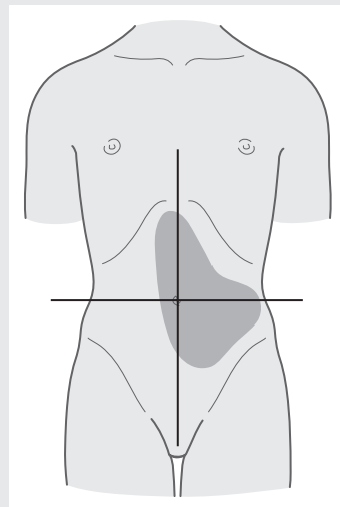

Fig. 6.25 The position of pain associated with irritable bowel syndrome

Diverticulitis

The incidence of diverticulitis increases with increasing age. It is most prevalent in the elderly and is characterised by constant pain and local tenderness. Pain is more commonly seen in the left lower quadrant (Fig. 6.26) but can be suprapubic and occasionally in the right lower quadrant. Pain tends to be cramp-like in nature. Fever is a prominent feature and altered bowel habit is usual with diarrhoea more common than constipation.

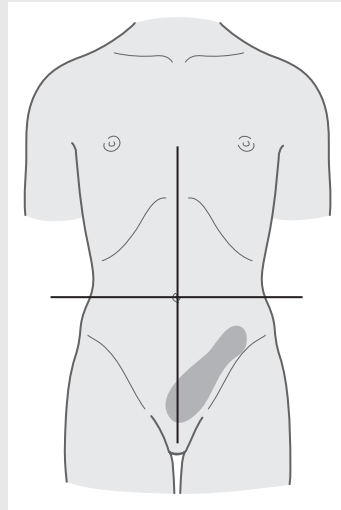

Fig. 6.26 The position of pain associated with diverticulitis

Intestinal obstruction

Intestinal obstruction is most prevalent in people over the age of 50. It has sudden and acute onset. The pain is described as colicky and can be experienced anywhere in the lower abdomen. Constipation and vomiting are prominent features. A patient with lower abdominal pain in the absence of constipation and vomiting is very unlikely to have an intestinal obstruction.

Appendicitis

Classically, the pain starts in the mid-abdomen region, around the umbilicus, before migrating to the right lower quadrant after a few hours (Fig. 6.27), although right-sided pain is experienced from the outset in about 50% of patients. The pain of appendicitis is described as colicky or cramp-like but after a few hours becomes constant. Movement tends to aggravate the pain and vomiting might also be present. Appendicitis is most common in young adults, especially young men. The absence of right lower quadrant pain and a history that the person has suffered similar pain previously should eliminate appendicitis from any differential diagnosis.

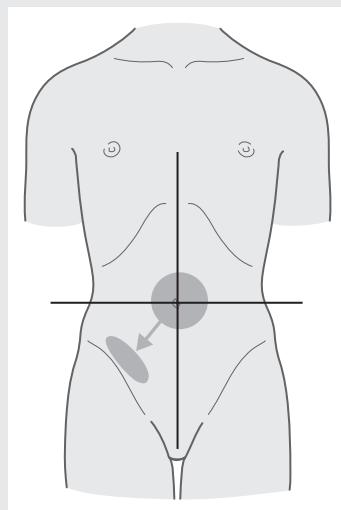

Fig. 6.27 The position of pain associated with appendicitis

Conditions affecting women

Generalised lower abdominal pain can be experienced in a number of gynaecological conditions (Fig. 6.28):

- Ectopic pregnancy: patients suffer from persistent moderate to severe pain that is sudden in onset. A menstrual history will reveal that the patient's last period is late. Additionally, 80% of patients will experience bleeding ranging from spotting to the equivalent of a menstrual period. Any patient who is sexually active, with abdominal pain whose period is late should be referred.
- Salpingitis (inflammation of the fallopian tubes): occurs predominantly in young, sexually active women, especially those fitted with an IUD. Pain is usually bilateral and cramping. Pain starts shortly after menstruation and can worsen with movement.
- Endometriosis: patients experience lower abdominal aching pain that usually starts 5 to 7 days before menstruation begins and can be constant and severe. The pain often worsens at the onset of menstruation. Referred pain into the back and down the thighs is also possible.

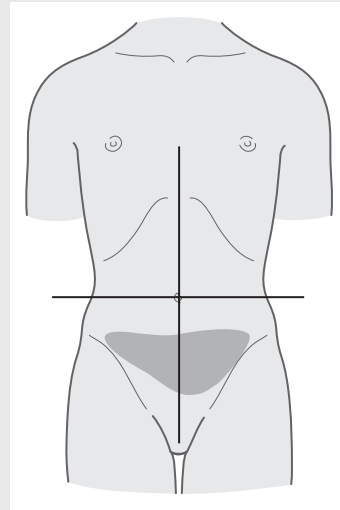

Fig. 6.28 The position of pain associated with women's conditions

Diffuse abdominal pain

A number of conditions will present with diffuse abdominal pain over the four quadrants. The most common cause of diffuse pain that will be seen by the pharmacist is gastroenteritis. Other causes include peritonitis and pancreatitis.

Gastroenteritis

Other symptoms of nausea, vomiting and diarrhoea will be more prominent in gastroenteritis than abdominal pain. The patient might also have a fever and suffer from general malaise.

Peritonitis

Although the pain of acute peritonitis can be diffuse, severe pain in the upper abdomen is often present. This is accompanied by intense rigidity of the abdominal wall producing a 'board-like' appearance; vomiting might also be present.

Figure 6.29 will aid in the differentiation of the different types of abdominal pain.

TRIGGER POINTS indicative of referral: Abdominal pain

- Abdominal pain with fever
- ALARM signs and symptoms:
  - Anaemia
  - Loss of weight
  - Anorexia
  - Recent onset of progressive symptoms
  - Melaena, dysphagia and haematemesis
- Elderly
- Pregnancy or suspected pregnancy
- Trauma
- Severe pain or pain that radiates
- Vomiting

Evidence base for over-the-counter medication and practical prescribing and product selection

The two conditions that have abdominal pain/discomfort as one of the major presenting symptoms and can be treated OTC are dyspepsia and IBS. For further information on products used to treat these conditions, please refer to pages 139–142 and 157–159.

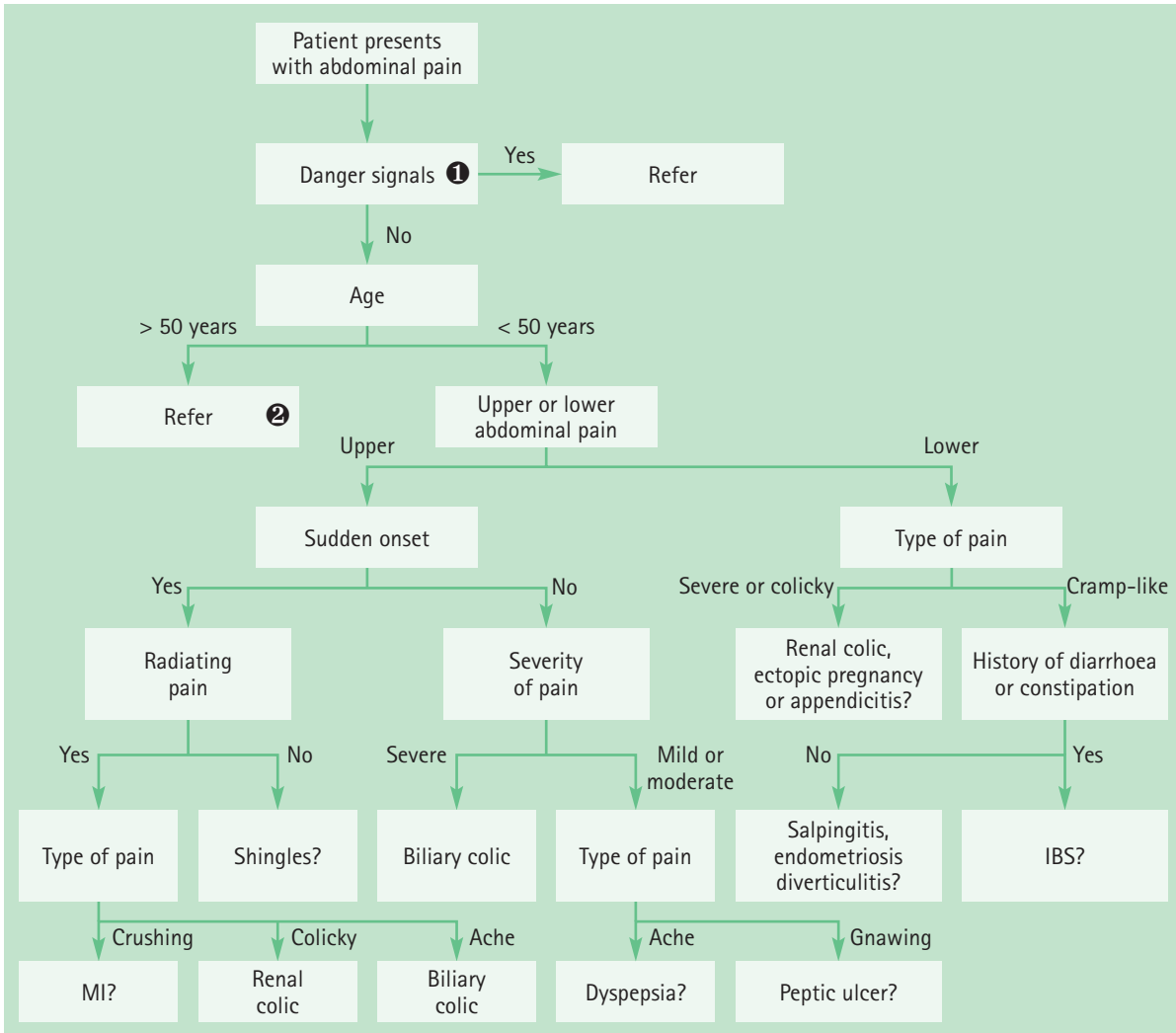

Fig. 6.29 Primer for differential diagnosis of abdominal pain

❶ Danger signals are significant bleeding, vomiting and fever.

❷ Organic disease is more likely to be the cause of abdominal pain in patients aged over 50, especially if symptoms are new or more severe than normal.

Further reading

Bagshaw EJ. Abdominal pain protocol: right upper quadrant pain. Lippincotts Prim Care Pract 1999;3:486–92.
Guthrie E, Thompson D. Abdominal pain and functional gastrointestinal disorders. BMJ 2002;325:701–3.
Kalloo AN, Kantsevoy SV. Gallstones and biliary disease. Prim Care 2001;28:591–606.
Lucenti MJ, Nadel ES, Brown DF. Right lower quadrant pain. J Emerg Med 2001;21:431–4.

Web sites

Prodigy guidance on renal colic: http://cks.library.nhs.uk/renal_colic_acute
The Pancreatitis Supporters' Network: http://www.pancreatitis.org.uk/

Self-assessment questions

The following questions are intended to supplement the text. Two levels of questions are provided: multiple choice questions and case studies. The multiple choice questions are designed to test factual recall and the case studies allow knowledge to be applied to a practice setting.

Multiple choice questions

6.1 Which one of the following statements about gastric ulcers is false?

- **a.** The pain is often aggravated by caffeine
- **b.** The pain is localised
- **c.** Symptoms tend to be episodic
- **d.** Endoscopical findings are usually positive for *H. pylori*
- **e.** Weight loss is common

6.2 In the treatment of constipation which one of the following statements is true?

- **a.** Bulk-forming laxatives usually act within 12 to 24 hours
- **b.** Senna tablets should be avoided in nursing mothers
- **c.** Fybogel is not suitable for a patient with coeliac disease
- **d.** Lactulose should not be taken by diabetic patients
- **e.** Liquid paraffin has been linked with causing lipid pneumonia

6.3 A man asks for the best thing to stop diarrhoea as he is going on holiday and he doesn't want to be caught short. Which of the following is the first-line treatment to be recommended?

- **a.** Kaolin and morphine
- **b.** Rehydration solution
- **c.** Antibiotics
- **d.** Antispasmodics
- **e.** Loperamide

6.4 Antacids that contain aluminium, calcium or magnesium salts inhibit the intestinal absorption of which of the following?

- **a.** Chloramphenicol
- **b.** Cephalexin
- **c.** Erythromycin
- **d.** Tetracycline
- **e.** Phenoxymethylpenicillin

6.5 What condition predisposes patients to oral thrush?

- **a.** Heart failure
- **b.** Asthma
- **c.** Diabetes mellitus
- **d.** Hyperlipidaemia
- **e.** Parkinson's disease

6.6 Abdominal pain that starts centrally then moves to the right lower quadrant is indicative of?

- **a.** Irritable bowel syndrome
- **b.** Pancreatitis
- **c.** Pyelonephritis
- **d.** Appendicitis
- **e.** Renal colic

6.7 Which condition is least likely to cause rectal bleeding?

- **a.** Haemorrhoids
- **b.** Crohn's disease
- **c.** Colorectal cancer
- **d.** IBS
- **e.** Anal fissure

6.8 Which one of the following preparations would not be used for the treatment of pain-free gingivitis?

- **a.** Corsodyl mouthwash
- **b.** Eludril mouthwash
- **c.** Corsodyl gel
- **d.** Bocasan
- **e.** Difflam mouthwash

Questions 6.9 to 6.11 concern the following conditions:

- **A.** Irritable bowel syndrome
- **B.** Constipation
- **C.** Diarrhoea
- **D.** Haemorrhoids
- **E.** Dyspepsia

Select, from A to E, which statement best relates to the conditions above

6.9 Is characterised with epigastric pain

6.10 Can be treated with antispasmodics

6.11 Is associated with left lower quadrant pain

Questions 6.12 to 6.14 concern the following OTC medications:

A. Gaviscon liquid
B. Asilone suspension
C. Milk of magnesia
D. Sodium bicarbonate powder
E. Aludrox liquid

6.12 Is most suitable for treating heartburn, which tends to get worse when lying down

6.13 Is most suitable to treat abdominal discomfort caused by trapped gas

6.14 Could be used to relieve constipation, as well as indigestion

Questions 6.15 to 6.17: for each of these questions *one or more* of the responses is (are) correct. Decide which of the responses is (are) correct. Then choose:

A. If a, b and c are correct
B. If a and b only are correct
C. If b and c only are correct
D. If a only is correct
E. If c only is correct

Directions summarised

A	B	C	D	E
a, b and c	a and b only	b and c only	a only	c only

6.15 When questioning a patient seeking advice for nausea and gastrointestinal upset, which of the following symptoms would indicate the need for direct referral to the general practitioner?

a. Feeling of impending vomiting
b. Loss of appetite over the last 24 hours
c. Dark coloured vomit

6.16 A common presentation of minor aphthous ulcers is

a. Pain
b. Ulcers on the buccal mucosa and tongue
c. Occur in crops of between one and five

6.17 Which symptoms in a patient presenting with constipation should be referred?

a. Melaena
b. Greater than 7 days duration
c. Abdominal pain

Questions 6.18 to 6.20: these questions consist of a statement in the left-hand column followed by a statement in the right-hand column. You need to:

- decide whether the first statement is true or false
- decide whether the second statement is true or false

Then choose:

A. If both statements are true and the second statement is a correct explanation of the first statement
B. If both statements are true but the second statement is NOT a correct explanation of the first statement
C. If the first statement is true but the second statement is false
D. If the first statement is false but the second statement is true
E. If both statements are false

Directions summarised

	1st statement	2nd statement	
A	True	True	2nd statement is a correct explanation of the first
B	True	True	2nd statement is not a correct explanation of the first
C	True	False	
D	False	True	
E	False	False	

	First statement	*Second statement*
6.18	IBS is common in people under the age of 40	It is caused by stress
6.19	Gingivitis is caused by plaque build-up	It is characterised by swollen and red gums
6.20	Heartburn causes retrosternal pain	Sphincter incompetence is responsible for symptoms

Case study

CASE STUDY 6.1

Mrs SJ, a 28-year-old women, asks to speak to the pharmacist because she wants something for stomach ache. You find out that the pain is located in the lower and upper left quadrant, but mainly the upper quadrant.

a. From which conditions might she be suffering?

Reflux, non-ulcer dyspepsia, gastritis, primary dysmenorrhoea, endometriosis, irritable bowel syndrome, pancreatitis, renal colic, MI and herpes zoster.

Further questioning reveals Mrs SJ to be suffering with pain she describes as 'an ache'.

b. Name the likely conditions that she could be suffering from?

The use of the word 'ache' means you can rule out those conditions that present with severe, stabbing, burning or gnawing pain:

- *pancreatitis, renal colic: severe*
- *reflux: burning*
- *herpes zoster: severe, lancing*

But it could still be any of: non-ulcer dyspepsia, gastritis, primary dysmenorrhoea, irritable bowel syndrome, endometriosis and MI. However, as the pain is primarily upper quadrant this makes primary dysmenorrhoea, endometriosis and irritable bowel syndrome less likely. This leaves non-ulcer dyspepsia, gastritis and MI as possibilities

c. Which questions would now allow you to differentiate between these conditions?

MI is the most unlikely of the three conditions and one would expect the patient to have more severe symptoms. Questions asking about radiation of pain, previous history of similar symptoms and precipitating/relieving factors should be asked.

You reach the differential diagnosis of non-ulcer dyspepsia but before you make any recommendations, you ask if she takes any medication from the GP, her response is as follows:

- Paracetamol prn: She has taken this for 6 months for knee pain
- Atorvastatin 40 mg od: She has taken this for the last 3 years for familial hyperlipidaemia
- Naproxen 500 mg bd prn: She has taken this for 6 months for knee pain.

d. Which of these medications, if any, do you consider are contributing to Mrs SJ's pain? Explain your rationale.

Of the three medicines that Mrs SJ is taking, the one most likely to cause GI irritation is Naproxen. However, she has been taking this for the last 6 months and you would expect that dyspepsia symptoms would have been experienced already if she was going to have a reaction to Naproxen. It is therefore unlikely that Naproxen has caused the problem, unless the dose has recently been changed. Atorvastatin can also cause GI side effects but has been taken for the last 3 years and is therefore almost certainly not the cause of the symptoms. Paracetamol is not known to cause GI irritation so can also be ruled out. In conclusion it is likely that none of the medicines have caused Mrs SJ's symptoms.

CASE STUDY 6.2

Mr LR, a male patient (approximately 50 to 60 years old), presents to the pharmacy at lunch time asking for something for diarrhoea. The following questions are asked, and responses received.

Information gathering	Data generated
Presenting complaint (possible questions)	
Describe symptoms	Going to the toilet three or four times a day. Normal habit is once or twice
Nature of movements	Very watery
Duration	4 or 5 days
Other symptoms/ provokes	Generally feels a bit rough. Headache and has a temperature. Been getting some cramping pains
Blood noticed	No
Eaten anything different in day or so before diarrhoea appeared	No
Additional questions	No foreign travel Doesn't seem to be worse at any time of day
Previous history of presenting complaint	Has had the odd bout of diarrhoea before but usually clears up after a couple of days
Past medical history	None
Drugs (OTC, Rx and compliance)	Ibuprofen 600 mg tds; aspirin 75 mg od; atenolol 25 mg od No change to medicines for last 6–9 months
Allergies	None known
Social history	
Smoking Alcohol Drugs Employment Relationships	Alcohol mostly at weekends. Does not smoke. Tries to exercise twice a week. Married
Family history	No-one in family with similar symptoms
On examination	General appearance is of a healthy person. No obvious signs of dehydration. Pinch test normal

Epidemiology dictates that the most likely cause of diarrhoea seen in primary care is bacterial or viral infection. However, other conditions are possible and are noted below:

Probability	Cause
Most likely	Viral and bacterial infection
Likely	Medicine induced
Unlikely	Irritable bowel syndrome, giardiasis, faecal impaction
Very unlikely	Ulcerative colitis and Crohn's disease, colorectal cancer, malabsorption syndromes

Diagnostic pointers with regard to symptom presentation

The expected findings for questions when related to the different conditions that can be seen by community pharmacists are summarised on the following page.

Continued

CASE STUDY 6.2

	Age	Acute or chronic	Timing	Periodicity	Weight loss	Blood in stools
Infection	Any	Acute	Any	Acute	No	Unusual
Medicines	Any	Acute or chronic	Any	No	No	No
IBS	<45 years	Acute	Mornings?	Recurs	No	No
Giardiasis	Any	Acute	Any	Acute	No	No
Faecal impaction	Elderly	Chronic	Any	No	No	No
Ulcerative colitis	Young adults	Acute	AM and PM	Recurs	No	Yes
Crohn's disease	Young adults	Acute	AM and PM	Recurs	No	Yes
Coeliac disease	Infants or middle-aged	Chronic	Any	No	Yes	No
Carcinoma	>50 years	Chronic	Any	No	Yes	Unusual

When this information is applied to that gained from our patient (below) we see that from the questions asked the most likely cause of his symptoms is infection.

	Age	Acute or chronic	Timing	Periodicity	Weight loss (not asked)	Blood in stools
Infection	✓	✓	✓	✓	?	✓?
Medicines	✓	✓	✓	✗	?	✓
IBS	✗	✓	✗?	✓	?	✓
Giardiasis	✓	✓	✓	✓	?	✓
Faecal impaction	✗	✗	✓	✗	?	✓
Ulcerative colitis	✗	✓	✗	✓	?	✗
Crohn's disease	✗	✓	✗	✓	?	✗
Coeliac disease	✓	✗	✓	✗	?	✓
Carcinoma	✓	✗	✓	✗	?	✓?

CASE STUDY 6.2

Danger symptoms/signs (trigger points for referral)

As a final double check it might be worth making sure the person has none of the 'referral signs or symptoms'; this is the case with this patient.

Change in bowel (long term) habit in patients over 50	✗
Diarrhoea following recent travel to tropical or subtropical climate	✗
Duration longer than 2 to 3 days in children and elderly	N/A
Patients unable to drink fluids	?
Presence of blood or mucus in the stool	✗
Signs of dehydration	✗
Severe abdominal pain	✗
Steatorrhoea	✗
Suspected faecal impaction in the elderly	N/A

The question mark against 'unable to drink fluids' should be determined during advice and product selection, and so in this context is not applicable.

CASE STUDY 6.3

Mrs RH, an elderly patient (about 75 years old), picks her prescription up and at the same time says she wants something to help get rid of a funny patch on the inside of her cheek. The following questions are asked, and responses received.

Information gathering	Data generated
Presenting complaint (possible questions)	
Describe symptoms	White patch about the size of a 10 pence piece
How long have you had the symptoms	Had for a couple of weeks
Type/severity of pain	Not really painful
Other symptoms/ provokes	No other obvious symptoms
Additional questions	No systemic symptoms (e.g. fever, chills)
Previous history of presenting complaint	Had something similar a couple of years ago and the other chemist gave me some cream
Past medical history	RA, HT, stroke 2 years ago
Drugs (OTC, Rx and compliance)	Ibuprofen 600 mg tds; aspirin 75 mg od; dipyridamole 200 mg bd; atenolol 25 mg od
Allergies	None known
Social history	
Smoking Alcohol Drugs Employment Relationships	Lives on her own and watches TV most of the time. Loves quiz shows
Family history	
On examination	Discrete white patch. No underlying redness

Epidemiology dictates that the most likely cause of white patches in the oral cavity seen in primary care is thrush. However, other conditions are possible and are noted below:

Probability	Cause
Most likely	Thrush
Likely	Minor aphthous ulcers, medicine induced, ill-fitting dentures
Unlikely	Underlying medical disorders, e.g. diabetes, xerostomia (dry mouth) and immunosuppression, major & herpetiform ulcers, herpes simplex
Very unlikely	Leukoplakia, squamous cell carcinoma

Diagnostic pointers with regard to symptom presentation

The expected findings for questions when related to the different conditions that can be seen by community pharmacists are summarised on the following page.

CASE STUDY 6.3

	Number	Location	Size and shape	Age	Pain
Thrush	'Single patch'	Anywhere	Irregular and variable size	Young and elderly	No
Minor ulcers	Up to five or so ulcers	Lips and inside cheeks	Less than 1 cm and round	10–40 years most common	Yes
Major ulcers	Numerous	Anywhere	Large (and variable shape)	All ages	Yes
Herpetiform	Very numerous	Back of the mouth	Pinpoint & round	All ages	Yes
Herpes simplex	Numerous	Anywhere	Small	Children	Yes
Lichen planus	Diffuse	Tongue, cheek, gums	'Spider's web'	Adults	No
Leukoplakia	Singular patch	Tongue or cheek	Irregular and variable size	Elderly	No
Carcinoma	Singular lesion	Tongue, mouth, lower lip	Irregular and variable size	Elderly	No, but latter stages yes

When this information is applied to that gained from our patient (below) we see that from the questions asked the diagnosis is either thrush, lichen planus or leukoplakia. Lichen planus can be ruled out because of the appearance of the white patch (plus lichen planus also commonly has a rash, but not always). This leaves a diagnosis between thrush and leukoplakia. Although the lady is not really complaining of pain, there is a possibility that this 'white patch' could be deemed potentially sinister, especially as she is of an age where leukoplakia is more likely. A positive smoking history would make leukoplakia even more of a possibility. This person must be referred.

	Number	Location	Size and shape	Age	Pain
Thrush	✓	✓	✓	✓	✗
Minor ulcers	✗	✓	✗	✗	✗
Major ulcers	✗	✓	✗	✗?	✗
Herpetiform	✗	✗	✗	✓	✗
Herpes simplex	✗	✓	✗	✗	✗
Lichen planus	✓?	✓	✓	✓	✓?
Leukoplakia	✓	✓	✓	✓	✓
Carcinoma	✗?	✓	✓	✓	✓?

Answers to multiple choice questions

1 = c	2 = e	3 = b	4 = d	5 = c	6 = d	7 = d	8 = e	9 = e	10 = a
11= a	12 = a	13 = b	14 = c	15 = e	16 = a	17 = d	18 = c	19 = b	20 = a.