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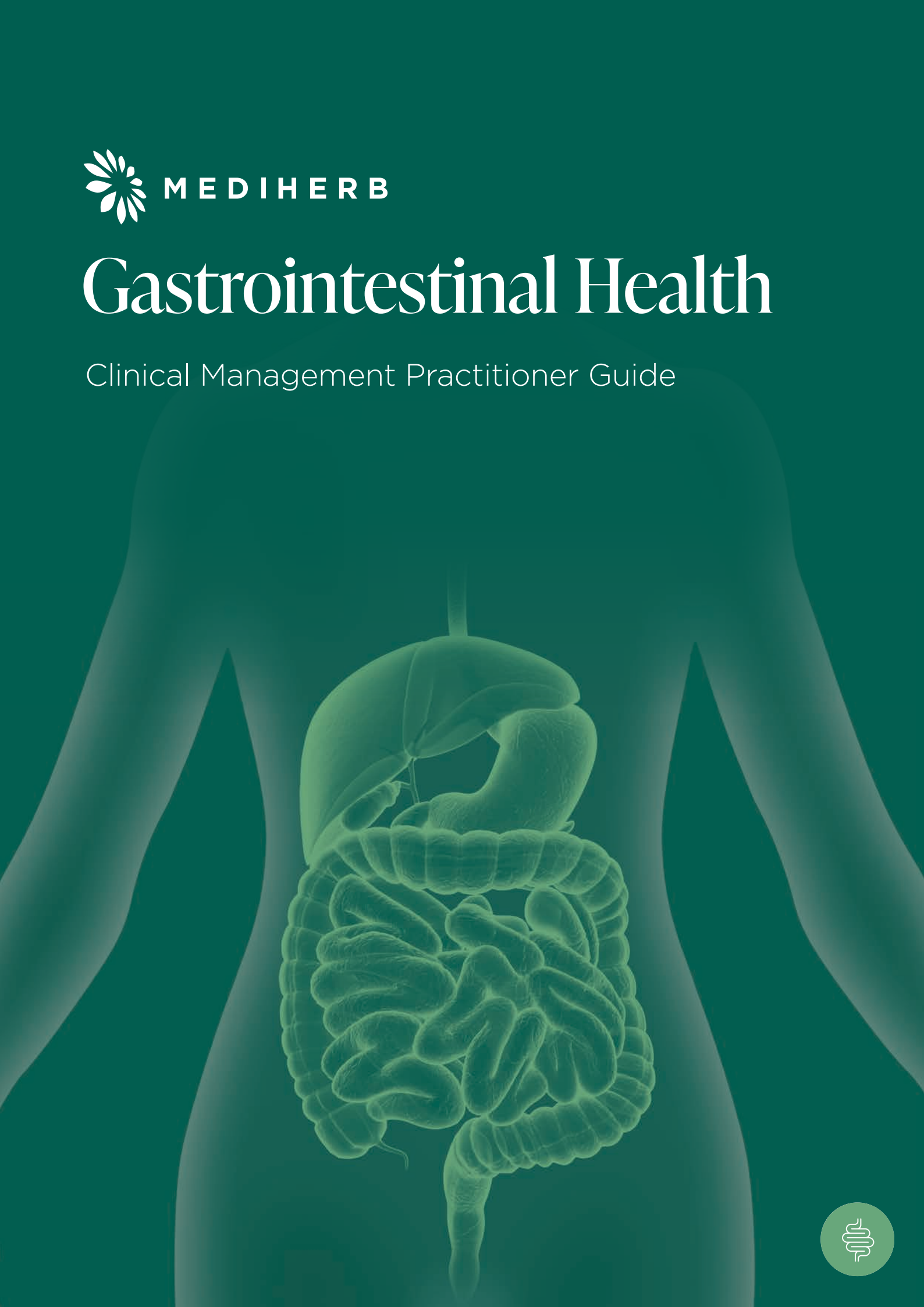
Gastrointestinal Health

Clinical Management Practitioner Guide



Introduction

Connecting back to the Hippocratic understanding that "all disease begins in the gut", the gastrointestinal tract (GIT) is considered the basis for all health and disease, in naturopathic medicine.

The GIT extends from mouth to anus and includes supporting glandular structures, the gut microbiome, the immune system, and the nervous system. The GIT is therefore central to overall health. As naturopaths and herbalists have an intimate understanding of GIT health and dysfunction, they are well placed to support patients by offering specialised nutrients, herbs, probiotics, diet, and lifestyle interventions to promote healing and restore optimal GI function.

This booklet covers common clinical presentations involving the GIT, including naturopathic considerations/therapeutic goals and suggested herbs and nutrients to support a wholistic treatment plan for your patient.

Iberis amara

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Diverticular disease

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Naturopathic Considerations/Therapeutic Goals

General Management Considerations

- Modify dietary factors that contribute to symptomatic disease progression e.g. low fibre intake
- Modify lifestyle factors that contribute to disease progression e.g. obesity
- Improve transit time
- Regulate colonic motility
- Reduce intra-colonic pressure
- Down-regulate low grade inflammation
- Support a healthy microbiome

Symptomatic Considerations*

- Soothe and heal the gastrointestinal mucosa
- Address infection/SIBO (if present)
- Down-regulate inflammation/ relieve pain

*Complications of diverticulitis can be a medical emergency, ensure that the patient has been assessed by their GP or specialist prior to prescribing.

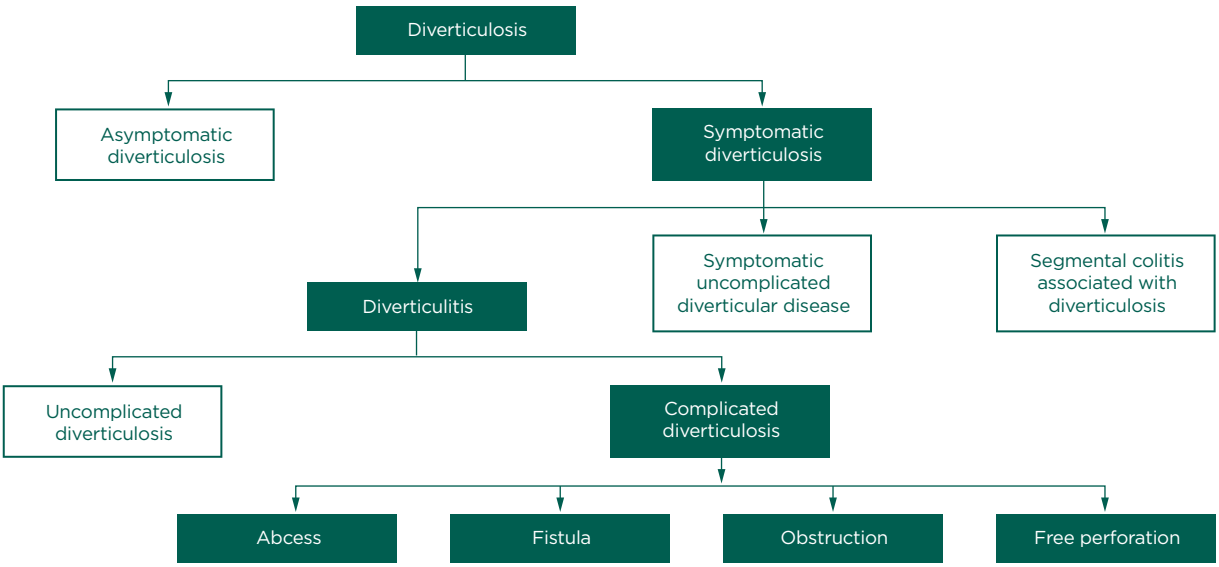
Overview

Being one of the most prevalent conditions of the Western world, the incidence of diverticular disease has increased dramatically over the past century.[1,2] While traditionally thought to be a disease associated with the elderly, the incidence of younger patients (40 years or younger) is on the rise.[2]

Diverticular disease encompasses several classifications:[1,3]

- **Asymptomatic diverticulosis** – Generally, an incidental finding from investigation for other conditions. It is characterised by the presence of diverticular (small outpouchings) in the intestinal wall.
- **Diverticulitis (complicated and uncomplicated)** – A common complication of diverticulosis, resulting from inflammation of the diverticulum, this can be acute or chronic. Complicated refers to the formation of fistulas, abscesses, obstruction or perforation.
- **Symptomatic uncomplicated diverticular disease, which includes:**
  - Chronic recurrent diverticulitis
  - Segmental colitis associated with diverticulosis – Considered distinct from diverticulosis, it does not specifically involve inflammation of the diverticular orifice, but rather the presence of multiple diverticular surrounding non-specific, segmental inflammation of the sigmoid colon.
  - Symptomatic uncomplicated diverticular disease (SUDD) – SUDD involves chronic abdominal pain without the presence of acute diverticulitis symptoms or obvious colitis.

Figure 1 | Classification of diverticular disease[1]

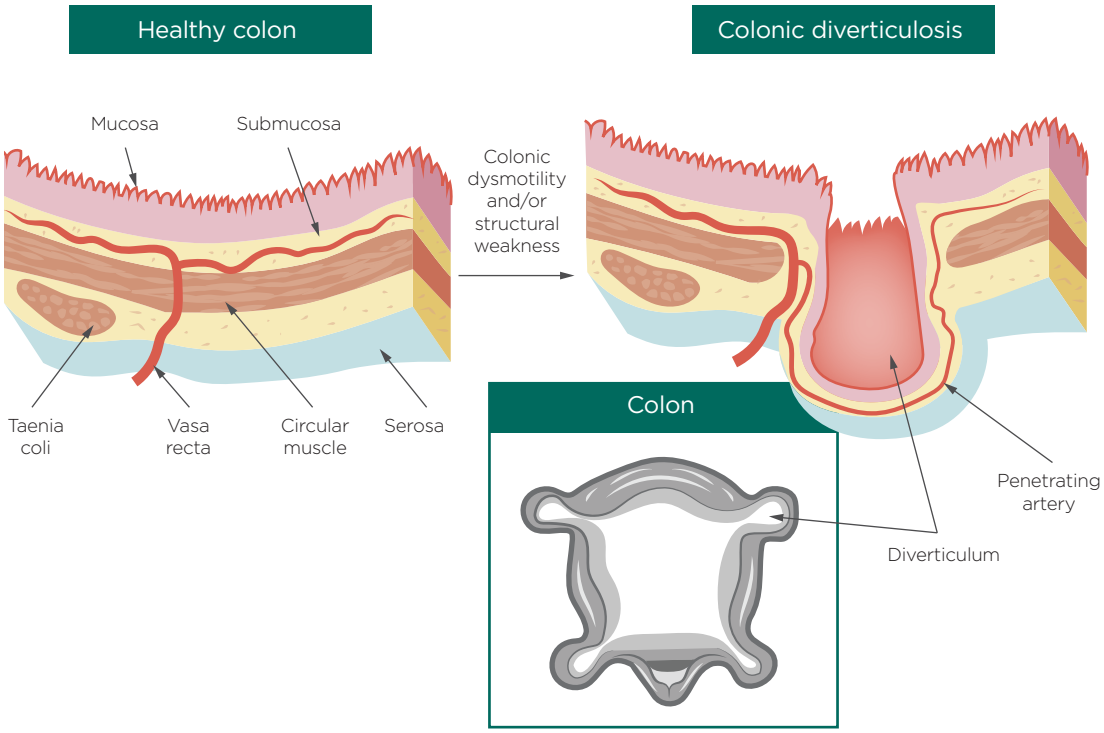


Aetiology & Pathophysiology

The pathogenesis of diverticular disease is considered to be multifactorial and while not completely understood, it is postulated that a combination of genetic and environmental factors, including a lack of dietary fibre, contribute to the formation of mucosal herniations in the colon wall.[1] Ten to twenty five percent of patients with diverticulosis will go on to develop diverticulitis.[1]

- **Colonic wall structural abnormalities** – Diverticular generally form at weaker areas of the bowel, between the mesenteric and antimesenteric teniae, where the muscle is penetrated by the *vasa recta*.[4] Compared to healthy controls, the colonic wall affected by diverticular disease has circular muscle thickening from abnormal deposition of elastin, as well as shortening of the taenia (elastin content is increased more than 200% in diverticular disease). Narrowing of the lumen is also observed. In addition, abnormal collagen cross-linking has been noted making the stiffer tissue more susceptible to tears, particularly in the presence of increased luminal pressures.[4]

Figure 2 | Comparison of healthy colon to colonic diverticulosis[5]



- **Motility dysfunction** – It is also postulated that alterations in intestinal motility may contribute to the pathogenesis of diverticular disease. More pronounced contractions have been observed in some patients with diverticular disease, showing increased contractile activity and intraluminal pressure both after stimulation by meals and at rest.[6]

  Affected areas in patients with diverticular disease have also been shown to have significantly increased motility in comparison to controls, as well as a higher incidence of disorganised and retrograde propagation of propulsions.[4]

  In addition, it is noted that compared to a normal colon, the cholinergic nerves in a colon affected by diverticular are more strongly innovated, while the action of inhibitory nerves is lessened, as well as a reduced relaxatory action of nitric oxide.[4]

- **Low fibre intake** – Low fibre diets common in Western countries, are thought to be a contributing factor for the development diverticular disease. The decrease in dietary fibre intake in the Industrial Revolution lead to a significant increase in diverticular disease, first shown in adults (40 + years) who were children first raised on the new industrialised diet.[4]

  Although a high fibre diet is an established recommendation for diverticular disease, it is still debated. Regardless, a negative association between fibre consumption and diverticular disease development has been noted. Some research indicates that fibre increases transit time and bowel movements, lowers intracolonic pressure, increases stool weight and volume, and normalises motility.[4] In addition, it has been demonstrated that consumption of 20–30 g of bran a day limits disease progression and lowers intraluminal pressure.[7]

  A low fibre diet is also a risk factor for progression to diverticulitis, potentially from faecal stasis or impaction in the diverticular sac.[8] In addition, fibre is important for intestinal microbial diversity and short chain fatty acid (SCFA) production, which in turn supports the mucosal barrier and immunity.[8]

- **Genetics** – Twin studies reveal a strong genetic component in diverticular disease with monozygotic twins experiencing a 7-fold increased risk of developing diverticular disease if one's twin was affected, and a 3-fold risk in dizygotic twins compared with the general population.[1]

  Genetics also impacts the site of disease development. In Western countries, the sigmoid colon is the most common site of diverticulosis, however, in Asian countries, the right colon is more often affected. This difference is observed even after migration to Western countries and following a Westernised diet, indicating that genetics may play a large role in determining the weak areas of the bowel as well as a predisposition to diverticular disease itself.[1]

  In addition, the development of diverticulosis is associated with genetic connective tissue (CT) disorders such as Marfan Syndrome and Ehlers-Danlos syndrome.[9]

- **Chronic inflammation** – While acute inflammation is characteristic of diverticulitis, it is postulated that chronic low-grade inflammation can play a role in the early pathogenesis of diverticular disease, as well as predisposing patients to SUDD and progression to diverticulitis. Interestingly certain risk factors for the development of diverticulitis are also associated with low-grade inflammation, including; smoking, obesity, physical inactivity, and high red meat consumption.[8]

- **Low vitamin D status** – Mechanisms linking vitamin D to diverticular disease are demonstrated in animal studies, where supplementation has been found to support gastrointestinal immunity and barrier function, as well as modulating the inflammatory response.[10] Research into other diseases associated with vitamin D deficiency and disordered collagen and elastin, indicate that it has antifibrotic action, indicating a possible link between vitamin D deficiency, thickening of the colonic wall and diverticular disease.[11,12]

  Furthermore, large scale studies have found higher serum vitamin D levels in patients with uncomplicated diverticular disease compared with those requiring hospitalisation.[10,11] Patients with the lowest serum vitamin D levels had the most severe complications.[10]

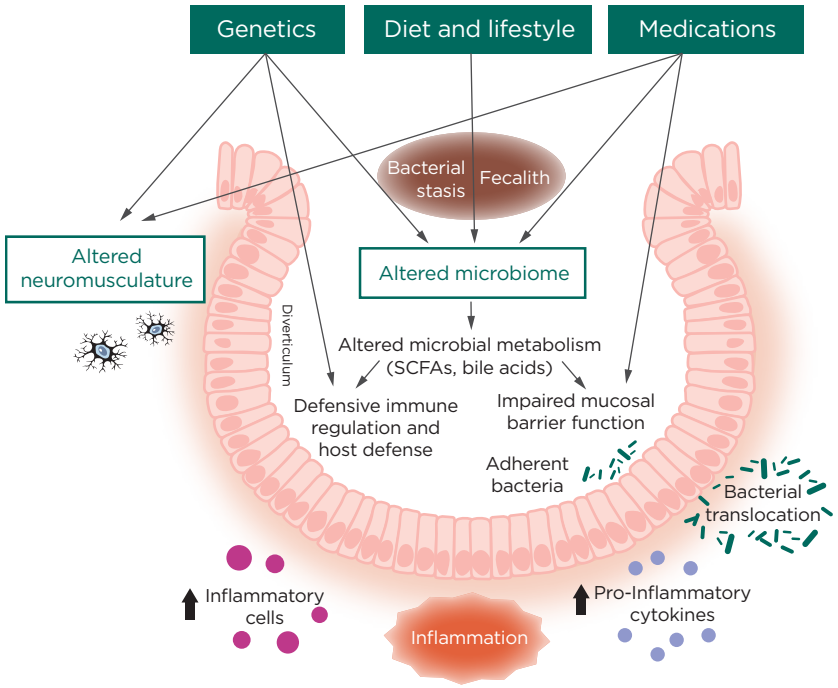
- **Dysbiosis** – Several studies have revealed reduced levels of SCFA producing bacteria such as *Clostridiales* spp., *Fusobacterium* spp. and *Lactobacillaceae* spp. and increased levels of pro-inflammatory bacteria such as *Marvinbryantia* spp. and *Subdoligranulum* spp. in patients with acute diverticulitis compared with controls.[8]

- **Non-steroidal anti-inflammatory use (NSAID)** – NSAID, aspirin and opiate use can increase the risk of developing diverticulitis and complications. A systematic review and meta-analysis found increased odds of perforation and abscess formation with opioid and NSAID use. While another review reported that NSAID and aspirin use significantly increased colonic diverticular bleeding.[13,14]

- **Obesity** – Obesity has been shown to be a risk factor for progression to diverticulitis. One study found that women with a body mass index (BMI) higher than 30 were 2 times more likely to experience complications of diverticulitis e.g. perforation and abscess.[15]

  In addition, waist to hip ratio has been shown to be an independent risk factor for complications. It is postulated that this is due to pro-inflammatory cytokine release from visceral fat, making central adiposity a key factor in disease progression.[15]

Figure 3 | Proposed pathophysiology of acute colonic diverticulitis[14]



Risk Factors for Development of Diverticular Disease

Non-controllable

- Age – incidence increases according to age with an estimated 30% of people aged 50 to 70, 50% of people aged 70 to 85 and 66% for those 85 years and older.[2]
- Genetics/ family member with diverticular disease.[8]
- Sex - diverticular disease is more common in men than women until the 6th decade of life, where it becomes more common in women.[14]
- Connective tissue disorders (collagen cross linking).[16]

Controllable

- Low fibre diet[14]
- High red meat intake (>116.6 g/day)[8,14,15]
- Low vitamin D status[14]
- SIBO[8]
- Dysbiosis[14]
- Smoking[15]
- Sedentary lifestyle[1]

Risk Factors for Progression to Diverticulitis/Complications/ Hospitalisation

- Obesity – body mass index, waist circumference and waist to hip ratio[1]
- Smoking[14]
- Sedentary lifestyle[14]
- Regular (≥ 2 x weekly) use of aspirin and other NSAIDs[1]
- Corticosteroid/opioid use[8]
- Use of oral contraceptives (OCP) or history of hormone replacement therapy (HRT)[8]
- Hypertension[8]
- Hyperlipidaemia[8]

Signs and Symptoms

For diverticulosis, there are often no clinical signs or symptoms[1], however, symptomatic diverticular disease signs and symptoms include:[3,8,17]

- Bloating
- Abdominal pain – often lower left quadrant
- Irregular bowel habits – diarrhoea or constipation
- Rectal bleeding

In some cases, patients may have both SUDD and IBS. As the symptoms of both can overlap, differentiation between what is causing the patient's symptoms can be challenging (is the diverticula causing symptoms or is it IBS).[7]

Differentiating symptoms of IBS, SUDD and diverticulitis[7,18]

IBS	SUDD	Diverticulitis
• Spasmodic pain related to bowel motion passage • Pain is generalised/diffuse • Relieved by passing stool/ flatulence	• Pain generally located in the left iliac fossa • Pain is sustained, lasting more than 24 hours, not relieved by passing stool • Pain can wake the patient at night	• Constant pain lasting several days, resolved by antibiotics • Fever associated with pain • Elevated white blood cell count

Symptoms of diverticulitis include:

- Peritonitis that is characterised by rebound tenderness, involuntary guarding, reduced or absent bowel sounds, abdominal distention[19]
- Fever[8]
- Vomiting[8]
- Inability to tolerate oral intake – food or fluids[8]

Complications

Mild cases of diverticulitis are often managed with antibiotics, however, more severe cases result in hospitalisation. It is considered one of the most common bowel related presentations to the emergency department.[20]

Complications include:[20]

- **Bleeding** – This can occur in diverticulosis (complicated and non-complicated) as the outpouchings are generally located where vessels penetrate the muscularis layer. Chronic diverticulitis can also present with bleeding.
- **Perforation** – Severe inflammation of the bowel wall can lead to loss of intestinal wall integrity and necrosis. While some perforations can be small and well contained, other non-contained perforations in acute diverticulitis can lead to the formation of fistula or abscesses. While a patient with intraperitoneal perforation can present with acute nausea, vomiting and abdominal pain, symptoms may be silent. This can lead to life threatening complications due to delayed diagnosis.
- **Abscess and phlegmon formation** - In cases of acute diverticulitis, abscess can occur in up to 30% of patients.
- **Fistula** – Can occur when an abscess breeches the intestinal wall after acute diverticulitis. Adjacent structures generally impacted include the bladder, ureter, uterus, fallopian tubes, vagina, adjacent intestinal sections and the perianal region.
- **Bowel obstruction** – While severe obstruction is rare, partial obstruction due to abscess formation, wall oedema, inflammation (acute) or intramuscular fibrosis (chronic) can occur.
- **Pylephlebitis (rare)** – An intra-abdominal infection complication, generally affecting the portal vein and/or its branches.

Differential Diagnosis[8,21–29]

Abdominal Pain	Diarrhoea	Constipation	Rectal Bleeding
Gastrointestinal			
• IBS • IBD • Colorectal cancer • Infection – bacterial, viral, parasitic • Appendicitis • Colitis • Coeliac disease • SIBO • Food intolerance	• IBS • IBD • Colorectal cancer • Infection – bacterial, viral, parasitic • Appendicitis • Coeliac disease • Microscopic colitis • SIBO • Lactose intolerance • Pancreatic insufficiency	• IBS • IBD • Colorectal cancer • Coeliac disease • SIBO	• IBD • Haemorrhoids • Anal fissure • Perianal abscess • Colorectal cancer • Polyps
Reproductive			
• Fibroid • Ectopic pregnancy • Endometriosis • Adenomyosis • Pelvic inflammatory disease • Ovarian torsion • Hydrosalpinx • Mittelschmerz	• Endometriosis	• Endometriosis • Fibroid	• Endometriosis
Genitourinary			
• Urinary tract infection • Interstitial cystitis • Chronic prostatitis • Urolithiasis			
Other			
• Abdominal adhesions	• Hyperthyroidism • Laxative use	• Hypothyroidism • Dehydration • Inadequate fibre intake • Medication use- opioids, iron, NSAIDs, antidepressants	

Diagnosis & Tests

Diagnosis is made with imaging techniques where the structure of the colonic wall can be visualised:

- Computed Tomography (CT) with intravenous contrast[3]
- Magnetic Resonance Imaging (MRI)[8]
- Ultrasound[8]
- Colonoscopy (although diverticulosis is often discovered via routine colonoscopy it is not recommended for acute diverticulitis due to the risk of bowel perforation).[8]

Other testing can indicate inflammation or infection. These tests are not specific for diverticular disease, but may assist in ruling out other conditions:

- Fecal calprotectin[8]
- C-reactive protein[8]
- Erythrocyte sedimentation rate[8]
- White cell count[8]
- Procalcitonin can indicate bacterial infection and sepsis[8]
- Vitamin D[8]
- Methane or hydrogen breath test (if SIBO is suspected).[8]

Associated Systems & Factors

The development of diverticulosis is associated with genetic connective tissue (CT) disorders such as Marfan Syndrome and Ehlers-Danlos syndrome as well non-genetic CT disorders including hernia, genital prolapse, aneurysms, and dislocation of the shoulder joint, indicating that generalised disordered collagen metabolism may underlie the development of diverticula.[9]

Herbal Medicine

General Management Considerations	Herbal Medicine
Improve transit time	Slippery elm, licorice, marshmallow
Regulate colonic motility	Slippery elm, globe artichoke, gentian, dandelion root, barberry
Reduce intra-colonic pressure	Slippery elm, partially hydrolysed guar gum (PHGG)
Down-regulate low-grade inflammation	Boswellia, turmeric, licorice, chamomile
Support a healthy microbiome	Slippery elm, marshmallow, garlic, acacia gum, pectin, cacao, red dragon fruit, PHGG

Symptomatic Considerations*	Herbal Medicine
Support and heal the gastrointestinal mucosa	Golden seal, licorice, marshmallow, slippery elm, myrrh, calendula
Address infection/SIBO (if present)	Golden seal, barberry, phellodendron, myrrh, garlic, propolis
Down-regulate inflammation/relieve pain	Boswellia, turmeric, licorice, chamomile

*complications of diverticulitis can be a medical emergency, ensure that the patient has been assessed by their GP or specialist prior to prescribing.

Slippery elm

- A demulcent that is soothing to the mucus membranes. Traditionally used for ulceration and inflammation of the gastrointestinal tract (GIT).[30]
- Contains water soluble and water-insoluble fibre.[30]
- Mucilages are traditionally used as a bulk laxative, increasing stool weight and act as a lubricating emollient.[30]
- Prebiotic to assist in the beneficial alteration of the colonic microbiota and production of SCFAs.[30]
- Stool cultures exposed to slippery elm increased in abundance of beneficial microbes including *Lactobacillus* spp. *Bifidobacterium* spp. and *Bacteriodes* spp. as well as an increase in butyrate-producing bacteria.[31]

Licorice

- Anti-inflammatory, mucoprotective, mild laxative, and demulcent. Traditionally used for mucous membranes including chronic gastritis and pepic ulcer.[32]
- Stool cultures exposed to licorice increased in beneficial bacteria and propionate-producing bacteria.[31]
- Promotes mucosal repair.[33]
- The constituent glycyrrhizin is attributed to anti-inflammatory action.[33]

Turmeric

- Anti-inflammatory, choleretic, carminative.[32]
- Animal studies have demonstrated curcumin to be protective against NSAID-induced mucosal damage in the upper GIT, however, considering its beneficial use in supporting remission in ulcerative colitis patients, a condition primarily affecting the colon and rectum, it is likely to have activity further down the GIT.[34,35]
- Modifies bowel flora increasing microbial richness and increasing abundance of beneficial *Bifidobacteria* spp. and *Lactobacilli* spp.[31,36,37]

Golden seal

- Traditionally used in Western herbal medicine for chronic inflammation of the mucous membranes and as a mucous membrane trophorestorative, antibacterial and antimicrobial.[32]
- Contains berberine. Animal studies have demonstrated the following benefits of berberine:[38,39]
  - Modulation of the microbiota in favour of a beneficial profile e.g. decreases Firmicutes:Bacteriodetes ratio.
  - Reduces intestinal permeability.
  - Reduces gastrointestinal inflammation.
  - Increase faecal SCFA content.
  - Anti-nociceptive (in a visceral pain model).

Nutritional Medicine

Assess vitamin D status of patient, supplement if required.

General Management Considerations	Herbal Medicine
Improve transit time	*Dietary fibre (*see Dietary considerations section*)
Regulate colonic motility	*Dietary fibre (*see Dietary considerations section*)
Reduce intra-colonic pressure	*Dietary fibre (*see Dietary considerations section*)
Down-regulate low-grade inflammation	N-acetylcysteine (NAC), Palmitoylethanolamide (PEA), omega-3 fatty acids, bioflavonoids, vitamin D
Support a healthy microbiome	Probiotics to support gut barrier function (*see page 13 for strains*)

Symptomatic Considerations*	Herbal Medicine
Support and heal the gastrointestinal mucosa	Glutamine, zinc carnosine, vitamin A, vitamin E, probiotics (*see below for strains*)
Address infection/SIBO (if present)	*Saccharomyces boulardii*
Down-regulate inflammation/relieve pain	NAC, PEA, vitamin D, probiotics (*see page 13 for strains*)

*Complications of diverticulitis can be a medical emergency, ensure that the patient has been assessed by their GP or specialist prior to prescribing.

Vitamin D

- Low Vitamin D levels have been shown in patients with diverticulitis, recurrence and complications.
- Animal models show that supplementation improves intestinal barrier function through regulation of tight junction proteins[40] and supports the gut immune response.[10]
- Supports mucosal immunity and the production of mucosal anti-microbial compounds such as cathelicidin.[40]

Probiotics

Various single-strain and multi-strain probiotics have been used as standalone therapy or in conjunction with pharmaceutical medication for diverticulitis symptom reduction and relapse avoidance. While a systematic review concluded that more research is warranted, 10 out of 11 trials reported improvement.[41]

- *B. bifidum* W23, *L. acidophilus* W37 and *L. brevis* W63 displayed a 90% level of protection of epithelial barrier damage induced by inflammatory cytokines.[42]
- *B. bifidum* W23, *B. lactis* W52, *L. acidophilus* W37, *L. brevis* W63, *L. casei* W56 and *L. lactis* W58 stimulate IL-10 production, preventing excessive pro-inflammatory responses.[42]

Zinc/zinc carnosine

- Reduces intestinal permeability in healthy subjects as well as in Crohn's disease.[43,44,45]
- Reduces aspirin-induced small bowel injury.[46]
- Is required for wound healing, supports matrix metalloprotein function and extra-cellular matrix remodelling.[47]
- Zinc transporter protein deficient animals display defects in connective tissue development.[48]

Glutamine

- Reduces intestinal permeability in healthy subjects.[49]
- Alters colonic bacteria producing a more favourable profile including a reduction in Firmicutes:Bacteriodetes ratio in humans.[50]
- Activates peroxisome proliferator-activated receptor gamma (PPAR-gamma), an endogenous regulator of gastrointestinal inflammation.[51]
- Glutamine plus probiotics reduces intestinal inflammation and oxidative stress; inhibiting nitric oxide (NO) and reducing inflammatory factors tumour necrosis factor alpha (TNF-α), IL-6, and IL-8.[52]

Dietary Considerations

A note on nuts

Historical recommendations to avoid nuts, seeds and popcorn in diverticular disease has recently been retracted. It was originally thought that these foods could become trapped in diverticular outpouchings increasing the risk of infection and obstruction there. In the Health Professionals Follow-up Study, researchers found an inverse association between nut and popcorn consumption and diverticular disease. Men consuming these foods at least twice per week had a significantly reduced risk of diverticulitis.[16]

- **Increase fibre intake**. It is demonstrated that consumption of 20–30 g of bran a day limits disease progression, normalises motility and lowers intraluminal pressure.[7]
- **Ensure adequate fluid consumption** to prevent constipation – 2.5 L daily.
- **Include bitter foods** such as rocket, dandelion, mustard greens, and radish to stimulate digestion and reduce transit time.
- **Include linseeds and psyllium husk powder** to provide lubrication of the GIT and reduce constipation.
- **Add prebiotic foods** to support the microbiome including; tomatoes, artichokes, bananas, asparagus, berries, garlic, onions, chicory, green vegetables, legumes, oats, linseed, and barley.
- **Reduce red meat intake** to <4 servings per week and avoid the intake of processed meat.[14]
- **Reduce inflammatory foods** including trans fats, refined foods and suspected/known intolerances e.g. gluten, dairy.
- **Include anti-inflammatory foods** such as high omega-3 fish, walnuts, ginger, and turmeric.
- **Increase consumption of fruit and whole grains.** Apples, pears, and prunes are most protective.[16,53]

Lifestyle Considerations

- **Increase physical activity.** One study in men found that sitting for at least 52 hours a week increased the chance (30%) of developing diverticulosis compared to men sitting for less than 16 hours a week.[15] In addition, vigorous physical activity (e.g. running if this is a realistic option), 2 hours a week has been linked to reduced diverticulitis incidence.[14]
- **Promote a healthy weight**, if indicated[1,15]
- **Avoid or reduce smoking**.[14]
- **Encourage healthy sun exposure** for vitamin D production e.g. mid-morning or afternoon for a short period in summer or a longer period around midday in winter (depending on the latitude).[54]
- **Avoid NSAIDs and corticosteroid use**.[13,14]
- Weigh up risk/benefits for **OCP and HRT use**.[8]

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Gastroesophageal Reflux Disease

Contents

Naturopathic Considerations/Therapeutic Goals

- Provide symptomatic relief
- Address contributing dietary factors e.g. food sensitivities
- Address contributing lifestyle factors e.g. achieve healthy body weight
- Soothe and heal the oesophagus
- Reduce oesophageal inflammation
- Promote lower oesophageal sphincter tone
- Promote gastric emptying
- Support the nervous system and reduce stress
- Increase antioxidant status to reduce risk of complications
- Address nutritional deficiencies associated with acid suppressing medication use (if indicated)

Overview

While regurgitation and heartburn is experienced by a large percentage of the population, gastro-oesophageal reflux is considered pathological when these symptoms cause complications and/or impact quality of life.[1] As such, gastroesophageal reflux disease (GORD) is defined as a 'condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications'.[2] GORD is estimated to occur in 10% to 15% of the Australian population.[3] This percentage is rising, with obesity identified as a key contributing factor.[3] As the pathophysiology of GORD is multifactorial, identifying the key contributing factors for each individual patient is paramount to tailored treatment and improved patient outcomes.[4]

Aetiology & Pathophysiology

The pathophysiology of GORD is related to a balance between aggressive and protective factors. Contact of acid, bile, pepsin, and duodenal contents with the oesophageal mucosa (aggressive factor) is key to the pathogenesis, along with failure of the protective mechanisms, which include, oesophageal acid clearance, the oesophago-gastric junction barrier and mucosal resistance.[1]

The following mechanisms are associated with GORD:

- **Lower oesophageal sphincter (LOS) dysfunction** – The LOS is located at the gastro-oesophageal junction and along with the diaphragm is involved in gastro-oesophageal sphincter competence. At rest, LOS maintains a high-pressure zone, which is above intragastric pressure, while relaxation of the LOS allows for the passing of food into the stomach. A constant low pressure allows for reflux to occur whenever intragastric pressure is higher than the LOS pressure. This constant low pressure occurs in a small amount of GORD sufferers and is generally associated with oesophagitis and other complications.[1]

  More commonly, the resting tone of the LOS is normal and patients experience an increased incidence of inappropriate LOS relaxations, which are unrelated to peristalsis or swallowing.[1] It is postulated that gastric distention triggered by stomach stretch receptors transient lower oesophageal sphincter relaxations (TLOSRs). Colonic fermentation of carbohydrates may also be a contributing factor.[2]

- **Oesophageal clearance** – A crucial protective mechanism is oesophageal acid clearance. Symptoms and the degree of mucosal damage is dependent on the length of time and degree of acid exposure to the oesophagus. Primary and secondary peristalsis is essential to the clearance of acid. Primary peristalsis is related to swallowing, while secondary occurs due to oesophageal distention or acidification. Another crucial element in acid clearance is the swallowing of saliva (containing salivary bicarbonate), which also restores oesophageal pH.[1]

  Patients with GORD have been shown to have longer acid clearance times, which may be attributed to an increased refluxate volume, peristaltic dysfunction (often associated with oesophagitis) or a reduced salivary rate.[1] It is important to note that cigarette smoking and anticholinergic drugs reduce salivation.[1,4]

- **Mucosal resistance** – An important factor to withstanding oesophageal injury is mucosal resistance. The mucosa of the oesophagus has both functional and structural components to provide protection including a pre-epithelial defence and an epithelial defence. The pre-epithelial defence, considered to be relatively weak, is composed of a water layer. This layer has a slight buffering capacity against pepsin, attributed to oesophageal submucosal gland secretions, as well as swallowed saliva.[1]

  Failure of the pre-epithelial defence falls back on the epithelial defence, which protects the oesophagus by limiting the rate of hydrogen ion penetration into the cell cytosol or intracellular space via the

intercellular junctional complex and cell membranes. In the event of intra-cellular pH becoming acidic, cell membrane ion transporters will remove acid from the cell cytosol or acid is neutralised through cellular and intercellular buffers.[1]

Mucosal injury is the result of aggressive factors overwhelming these defences.[1]

- **Delayed gastric emptying** – Delayed gastric emptying contributes to GORD through increasing the amount of refluxate leading to gastric distention. Gastric distention increases the rate of TLOSR, which can trigger postprandial GORD.[1]
- **Hiatal hernia** – A high proportion of patients with complications have a hiatal hernia, which hinders LOS function. In addition, during oesophageal acid clearance, acid containing material may become trapped in the hernia sac. As a result, when the patient swallows and the LOS relaxes, the contents flows back into the oesophagus.[1]
- **Acid pocket** – Refers to a pocket of highly acidic gastric contents close to the gastro-oesophageal junction that develops after ingestion of a meal. While the meal buffers the gastric contents in most of the stomach, the acid pocket in the proximal stomach does not combine with the gastric chyme and remains very acidic. Patients with GORD have a larger acid pocket, and if a hiatal hernia is present, the pocket may extend into the LOS creating more reflux in response to TLOSRs.[5]

Risk Factors

Non-modifiable[6]

- Genetics
- Age (more likely to affect those in the 35–59 age bracket)
- Sex (women)
- Pregnancy

Modifiable[7]

- Obesity
- Metabolic syndrome
- Smoking
- Stress/anxiety
- Medications
  - Oestrogen replacement therapy
  - Non-steroidal anti-inflammatories (NSAIDs)
  - Aspirin
  - Calcium channel blockers
  - Nitrates
  - Tricyclic antidepressants (clomipramine and amitriptyline in particular)
  - Hypnotics
  - Anticholinergics
  - Benzodiazepines
  - Theophylline

Signs and Symptoms[5,8]

- Heartburn (most common)
- Regurgitation (most common)
- Globus sensation
- Chest pain
- Belching
- Epigastric pressure/fullness
- Epigastric pain
- Chronic cough
- Bronchospasm
- Wheezing
- Hoarseness
- Sore throat
- Asthma
- Laryngitis
- Nocturnal choking
- Dental erosions

Alarm signs[8]

- Dysphagia
- Odynophagia
- Weight loss
- Iron deficiency anaemia

Complications

- Oesophagitis – inflammation of the oesophagus may lead to bleeding, erosions and scarring. Scarring is associated with dysphagia due to narrowing of the oesophageal sphincter.[5]

Long-term, unmanaged GORD can lead to more serious complications including:[5]

- Barrett's oesophagitis – long-term exposure to gastric acid can lead to pre-cancerous cellular changes in the oesophagus (squamous cells are replaced by columnar intestinal cells in the gastroesophageal junction).
- Oesophageal adenocarcinoma – a progression of Barrett's oesophagitis.

Differential Diagnosis

Symptoms such as dyspepsia, bloating, belching, and epigastric pain may also be a sign of the following:[8,9,10]

Dyspepsia	Heartburn	Bloating	Belching
• Peptic ulcer disease • Achalasia • Gastritis • Gastroparesis • Cholelithiasis • Chronic pancreatitis • Pancreatic/gastric cancer • Eosinophilic oesophagitis	• Eosinophilic oesophagitis	• Peptic ulcer disease • Achalasia • Gastritis • Gastroparesis • Dyspepsia	• Peptic ulcer disease • Achalasia • Gastritis • Gastroparesis • Dyspepsia
Epigastric pain	**Dysphagia**	**Odynophagia**	**Atypical Chest Pain**
• Peptic ulcer disease • Achalasia • Gastritis • Gastroparesis • Dyspepsia • Gastric cancer, • Acute pancreatitis • Cholelithiasis • Gastric cancer • Acute viral/alcoholic hepatitis • Acute pancreatitis • Eosinophilic oesophagitis	• Paraoesophageal hernia • Oesophageal adenocarcinoma • Achalasia • Radiation induced stricture • Oesophageal obstruction	• Infectious oesophagitis • Radiation-induced oesophageal injury • Pill oesophagitis	• Eosinophilic oesophagitis • Diffuse oesophageal spasm • Achalasia • Angina

Diagnosis and Tests

Generally, diagnosis is made through clinical symptoms and the patient's response to acid suppressing medication (antacids/H2 antagonists/ proton pump inhibitors [PPIs]). Upper endoscopy and esophageal pH monitoring are also used. Endoscopy is generally reserved for the presence of alarm symptoms, poor response to treatment, an unclear diagnosis or to rule out complications e.g. Barrett's esophagus.[8,11]

PPI non-responders

In non-responders to PPI therapy (about 30%), patients are found to have nonacidic or weakly acidic reflux.[12] While an estimated 50% of patients not taking PPI's have weakly acidic reflux.[2] One theory as to why weakly acidic reflux leads to symptoms, is that gas within the reflux causes proximal oesophagus distension. This leads to dilation of intercellular spaces, increasing mucosal permeability and thus causing heartburn.[2]

Associated Systems and Factors

In some cases, GORD may manifest as chronic/ recurrent otitis media (particularly in children), chronic sinusitis, and idiopathic pulmonary fibrosis.[2,13] Epidemiological studies also suggest that a high percentage of asthmatics have GORD (34% to 89%).[2] While debated, there may be a link between *Helicobacter pylori* infection and GORD.[14]

PPI/histamine type-2 (H2) antagonist/ antacid use and nutritional deficiencies

Utilised to both diagnose and treat GORD, patients may present with long-term use of PPI therapy. Long-term use of this medication is associated with certain nutritional deficiencies or reduced bioavailability including:[2,14,15,16]

- Vitamin B12
- Vitamin C
- Calcium
- Iron
- Magnesium

A traditional naturopathic understanding

A traditional theory is that GORD is caused by hypochlorhydria. While evidence supporting this idea is lacking, the theory is based on 2 potential mechanisms. Sufficient gastric acid is required for:[10]

- Adequate digestion of food to prevent fermentation and subsequent increased intragastric pressure
- To signal the LOS to remain closed

This has led to the traditional use of **bitters** as a treatment. Bitters may have therapeutic potential due to the following mechanisms:[10]

- Speeding gastric emptying
- Increasing saliva production
- Mucoprotective activity

It is important to note, however, bitters increase gastric acid secretion, which may exacerbate symptoms in some patients.[10] As such, the appropriateness of bitters is best assessed on a case by case basis.

Herbal Medicine

Therapeutic Goals	Herbal Medicine
Provide symptomatic relief	Marshmallow, licorice, slippery elm
Soothe and heal the oesophagus	Marshmallow, licorice, slippery elm, calendula, golden seal*
Reduce oesophageal inflammation	Licorice, turmeric, boswellia, meadowsweet
Promote lower oesophageal sphincter tone	Chaste tree (doses over 2 g/day)**, yarrow***, calendula***
Promote gastric emptying	Gentian*
Support the nervous system and reduce stress	Chamomile, lemon balm, skullcap, vervain, passionflower, withania, rhodiola, tinospora
Increase antioxidant status to reduce risk of complications	Rosemary, turmeric, grape seed, pomegranate

Slippery elm

- Slippery elm has been used as a demulcent for irritation and ulceration of the gastrointestinal tract (GIT) and to soothe the throat in traditional herbal medicine.[17]
- It contains mucilage that becomes a gel-like substance when mixed with water. Mucilages have been found to reduce local irritation and gastric inflammation.[17]

Meadowsweet

- Traditionally used in Western herbal medicine for disorders of the upper digestive tract e.g. reflux, indigestion and hyperacidity.[18]
- Antioxidant and anti-inflammatory.[19]

Licorice

- Anti-inflammatory, mucoprotective, demulcent.[18] Used in traditional Western herbal medicine for reducing mucosal irritation of the GIT.[20]
- Deglycyrrhizinised licorice (DGL) was found to significantly decrease dyspepsia in a clinical trial. Symptom improvement was found for upper abdominal fullness, upper abdominal pain, belching, bloating, nausea, vomiting, regurgitation, heartburn, and loss of appetite.[21]

Turmeric

- Anti-inflammatory and antioxidant action.[18]
- Curcumin prevented oesophageal mucosal damage from acute reflux esophagitis in an *in vivo* study.[22]
- Curcumin has shown to protect oesophageal epithelial cells exposed to exogenous acid *in vitro*. This was attributed to its anti-inflammatory activity.[22]

See A traditional naturopathic understanding (page 20).

**Chaste tree - at doses over 2 g (in 3 divided doses), chaste tree increases melatonin secretion.[23] Melatonin has been demonstrated to significantly increase LOS tone.[24]

***Herbs such as yarrow and calendula contain hydrolysable tannins, which may improve LOS tone.[10]

Nutritional Medicine

Therapeutic Goals	Nutritional Medicine
Soothe and heal the oesophagus	Zinc, glutamine
Reduce oesophageal inflammation	Bioflavonoids, quercetin, vitamin E, omega-3 fatty acids
Promote gastric emptying	*Lactobacillus reuteri* MM53, *Lactobacilli* spp., *Bifidobactium* spp.
Support the nervous system and reduce stress	Magnesium, B group vitamins
Increase antioxidant status to reduce risk of complications	N-acetylcysteine (NAC), vitamin E, quercetin, zinc, selenium, beta carotene
Address nutritional deficiencies associated with acid suppressing medication (if indicated)	Vitamin B12, vitamin C, iron, calcium, magnesium

Quercetin and vitamin E

- Lowered oesophageal inflammation, decreased acid and pepsin production increased glutathione and reduced collagen formation (indicating an antifibrotic effect) in experimentally-induced reflux oesophagitis.[2]

Beta-carotene

- A preliminary clinical trial reported significant reductions in GORD symptoms in patients with Barret's oesophagitis (25 mg/day for 6 months).[25]
- A significant reduction in the Barret's segment length was also reported.[25]

Probiotics

- A probiotic combination including *Bifidobacterium bifidum* W23, and *Bifidobacterium lactis* W52 reduced reflux episodes in pregnant women from 60% to 20% after 4 weeks of treatment.[26]
- *Lactobacilli* spp. and *Bifidobactium* spp. improve gastric emptying and may modulate TLOSR.[27]

Dietary Considerations

- **Eliminate exacerbating foods** – determine which foods cause symptoms in the patient and recommend avoidance. Common trigger foods include; orange/grapefruit juice, tomatoes/tomato preserves, spicy food, saturated fat/fried food, chocolate, carbonated beverages, coffee, and tea.[28]
- **Promote eating habits that reduce symptom risk** – reduce meal volume, cease eating meals before bed (leave a 2–3 hour gap), and ensure regular eating patterns.[28]
- **Low carbohydrate diet** – small scale studies suggest that a low carbohydrate diet reduces symptoms as colonic fermentation of carbohydrates can contribute to TLOSRs.[2]
- **Increase dietary fibre** – there is an inverse association between oesophageal adenocarcinoma and fibre intake.[29]
- **Increase dietary fruit, vegetables and antioxidants** - there is an inverse association between oesophageal adenocarcinoma and high intake.[29]

Lifestyle Considerations

- **Cease smoking** – smoking increases the risk of reflux. Potential mechanisms include; reduction of LOS pressure and prolonged oesophageal acid clearance.

  The incidence increases with the number of cigarettes smoked. Smoking contributes to the oxidative stress burden which can lead to complications and may reduce melatonin levels.[28,30,31]

  - **Vaping** - A case report discussed the exacerbation of controlled GORD after a patient vaped for 2 months. He presented with oesophagitis, with other causes being ruled out. It was concluded that the nicotine was likely to be a contributing factor, highlighting the importance of enquiring as to a patient's vaping history, as well as cigarette smoking.[32]

- **Encourage regular exercise** – a study exploring the lifestyle habits of patients with GORD found that a lack of exercise was associated with GORD, particularly in women, independent of body mass index (BMI).[33] While it has been reported that regular exercise has a protective effect,[33] the type of exercise is important. Strenuous exercise such as weight lifting can trigger symptoms, compared to exercise such as swimming, cycling or running, which may have a protective effect.[28] Another study reported that a regular post-dinner walk lowered the risk of postprandial symptoms of GORD.[34]
- **Reduce alcohol consumption** – alcohol contributes to GORD via multiple mechanisms; reduction of LOS pressure, increased TLOSRs, impairment of gastric emptying and oesophageal motility, and increased acid secretion.[30]
- **Encourage healthy weight loss** – mechanisms attributed to the high incidence of GORD in obesity include, increased abdominal pressure, increased TLOSR frequency, reduced resting LOS pressure and delayed gastric emptying. In addition, symptom incidence increases with BMI.[7]
- **Sleeping position** – as lying flat may contribute to reflux episodes, it is recommended to sleep with the head of the bed elevated. It has been found that sleeping on the left side of the body improves oesophageal clearance and nocturnal oesophageal pH.[30]

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Althaea officinalis

Inflammatory Bowel Disease

Contents

Naturopathic Considerations/Therapeutic Goals

Inflammatory Bowel Disease (IBD)	
• Reduce intestinal inflammation • Protect bowel mucosa • Improve antioxidant status • Address symptoms (diarrhoea, rectal bleeding, pain, fatigue, anorexia, weight loss)	• Address nutrient deficiencies (prevent anaemia and osteoporosis) • Maintain a healthy weight and muscle mass

	Ulcerative Colitis (UC)	Crohn's Disease (CD)
Therapeutic Goal	**Naturopathic Considerations/Therapeutic Goals**	
Improve barrier integrity	• Focus on mucoprotection	• Focus on gut wall healing
Address stealth pathogens	• Correct dysbiosis AND improve antiviral clearance	• Correct dysbiosis
Balance immune function	• Modulate immune response	• Improve innate immune response
Address symptoms	• Urgency, mucous secretion	• Perianal fissures, fistulas

Overview

Inflammatory bowel disease (IBD) encompasses several gastrointestinal (GI) diseases, the most common of which are ulcerative colitis (UC) and Crohn's disease (CD).

Considered diseases of autoimmunity, both are relapsing and remitting and involve infiltration of the intestinal wall by inflammatory cells, resulting in IBD lesions.[1] Both conditions present with diarrhoea, rectal bleeding, abdominal pain, fatigue, anorexia, and weight loss[2]; however, UC is often accompanied by a sense of urgency and increased mucous secretions, while abscesses and fistulas are a common presentation in CD.[3] In CD, inflammatory lesions can affect any part of the gastrointestinal tract (GIT) and are characterised by patchy distribution throughout the GIT.[1] Inflammation extends the entire thickness of the intestinal wall, leading to ulcers that can develop into abscesses and fistulae.[1] UC is confined to the rectum and colon, with inflammatory lesions only affecting the mucosa, sparing the deeper layers of the intestinal wall.[2] Table 1 details additional differentiating factors of UC and CD.

Table 1 | Clinical distinctions between ulcerative colitis and Crohn's disease.[3,4]

	UC	CD
Mucosal lesions	Microulcers and pseudo polyps more common, larger ulcers possible	Aphthous ulcers common in early stages; late disease notable ulcers with stellate, 'rake', 'bear-claw' linear or serpiginous ulcers; cobblestoning
Distribution	Continuous symmetric and diffuse, with granularity or ulceration found in involved segments	Discontinuous and asymmetric with skipped segments, normal intervening mucosa, especially in early disease
Rectum	Involving rectum and distributed proximally	Complete or relative rectal sparing may be present
Ileum	Not usually involved	Often involved (75% CD)
Depth of inflammation	Mucosal	Submucosal, mucosal, and transmural
Serosal findings	Absent, except in severe colitis or toxic megacolon	Marked erythema and creeping fat
Complications	Perianal findings not prominent	Perianal finding prominent, including large anal skin tags, deep fissures and complex perianal fistulas
Strictures	Rarely, suggestive of adenocarcinoma	Often present
Fistulas	Not present, except for rare cases	Perianal, enterocutaneous, rectovaginal, enterovescicular, and others
Granulomas	Should not be present	Present in 15% to 60% of patients
Histology	Crypt abscesses and ulcers are the defining lesion, ulceration on a background of inflamed mucosa	Crypt abscesses may be present, hallmark lesion is focally enhanced inflammation on a normal background
Serology	pANCA* positive in 60% to 65% of cases ASCA† positive in 5% of cases	pASCA positive in 20% to 25% of cases ASCA positive in 41% to 76% of cases

*Perinuclear antineutrophil cytoplasmic antibody (pANCA). †Anti-*Saccharomyces cerevisiae* antibody (ASCA).

Aetiology & Pathophysiology

The pathogenesis of IBD remains idiopathic, however, evidence suggests genetic, immunological and environmental factors initiate the autoimmune process.[5] It is thought in genetically susceptible individuals, IBD results from intestinal bacteria inappropriately and consistency activating an aberrant immune response, which is facilitated by defects in the barrier function of the intestinal epithelium and the mucosal immune system.[1,6]

- **Genetic predisposition** – 10 to 20 percent of UC patients report having a family member with UC, with the association highest among first-degree relatives and relatives of patients with early-onset disease. Both UC and CD are associated with HLA variants and multiple genes involved with immune signalling (especially interleukin (IL)-23 and IL-10). Several genetic polymorphisms are also associated with an increased risk of developing IBD including those related to the vitamin D receptor, IL and IL receptor gene. UC is associated with genetic defects in barrier function, while CD is associated with genetic defects in innate immunity and autophagy.[1,3]
- **Dysbiosis** – Alterations in intestinal microbiota are associated with the development of IBD,[3] as patients show reduced GI microbial diversity, primarily of Firmicutes, particularly, *Faecalibacterium prausnitzii*.[1] Functional changes in GI microbiota lead to a reduction in short chain fatty acid (SCFA) production and other anti-inflammatory metabolites that maintain and protect the mucosa; which are significantly decreased in IBD patients.[1] Other research has also found *Bacteroides fragilis* and *Bacteroides vulgatus* are decreased in patients with IBD, with *Bacteroides vulgatus* identified as the principal microflora present in healthy controls.[7] *Lactobacillus* spp. may also be reduced in active UC.[8]

#Located in the epithelium covering mucosa-associated lymphoid tissue, such as Peyer's patches of the small intestine.

Dysbiosis contributes to immune dysregulation in IBD via bacterial antigens, which are taken up by specialised microfold (M)# cells that pass between leaky epithelial cells or enter the lamina propria through ulcerated mucosa. These antigens are then presented to antigen-presenting cells (APCs), resulting in T cell activation and differentiation to a T helper type-1 (Th-1) mediated response via interferon-gamma (IFN-γ). This stimulates the inflammatory response and the release of other pro-inflammatory cytokines including IL-12, IL-23, IL-1, IL-6, and tissue necrosis factor-alpha (TNF-α).[1]

- **Altered serotonin signalling** – Serotonin (5-HT) is produced in the GI epithelium and is thought to act as a prominent regulatory molecule in both UC and CD, as extracellular 5-HT levels are increased during intestinal inflammation.[9] A 2020 study found that the serotonin reuptake transporter (SERT) is significantly reduced in inflamed areas of CD and UC.[9] The synthesis of tryptophan hydroxylase -1 is also compromised.[9] Defects in 5-HT signalling may therefore underline the altered motility, secretion and sensation in IBD.[10]

Pathophysiological mechanisms specific to UC:

- **Immune dysregulation in UC** – Altered immune function in UC results in mucosal inflammation and infiltration of macrophages and lymphocytes, up-regulating nuclear transcription factors, which trigger the release of pro-inflammatory mediators and cytokines, including TNF-α, IL-12 and IL-23, causing subsequent tissue damage.[1] The most common autoantibody in UC is the perinuclear antineutrophil cytoplasmic antibody (pANCA), which is found in most patients.[3] It is relatively specific (60% to 70%) for UC, however, it is not used in isolation for diagnosis.[11]
- **Deficient mucin** – Mucin protects and repairs the lining of the GIT and is often deficient in patients with UC, due to its active destruction by autoantibodies.[12] Reduced levels of mucin may lead to increased mucosal permeability making the mucosa more susceptible to bacteria and other luminal contents,[13] triggering the inflammatory process and immune dysregulation seen in UC.
- **Cytomegalovirus (CMV) infection** – An association between UC and CMV has been recognised for over 50 years, with an estimated 10% to 30% of IBD patients affected by CMV.[14] The role of CMV in UC is unclear, with controversy around whether the virus is a contributor or bystander, and if antiviral drug administration may alter the course of UC.[14] Reactivation of latent CMV is, however, increasingly recognised as an important clinical problem in patients with severe UC, especially in those receiving high doses of immunosuppression.[15]

Pathophysiological mechanisms specific to CD:

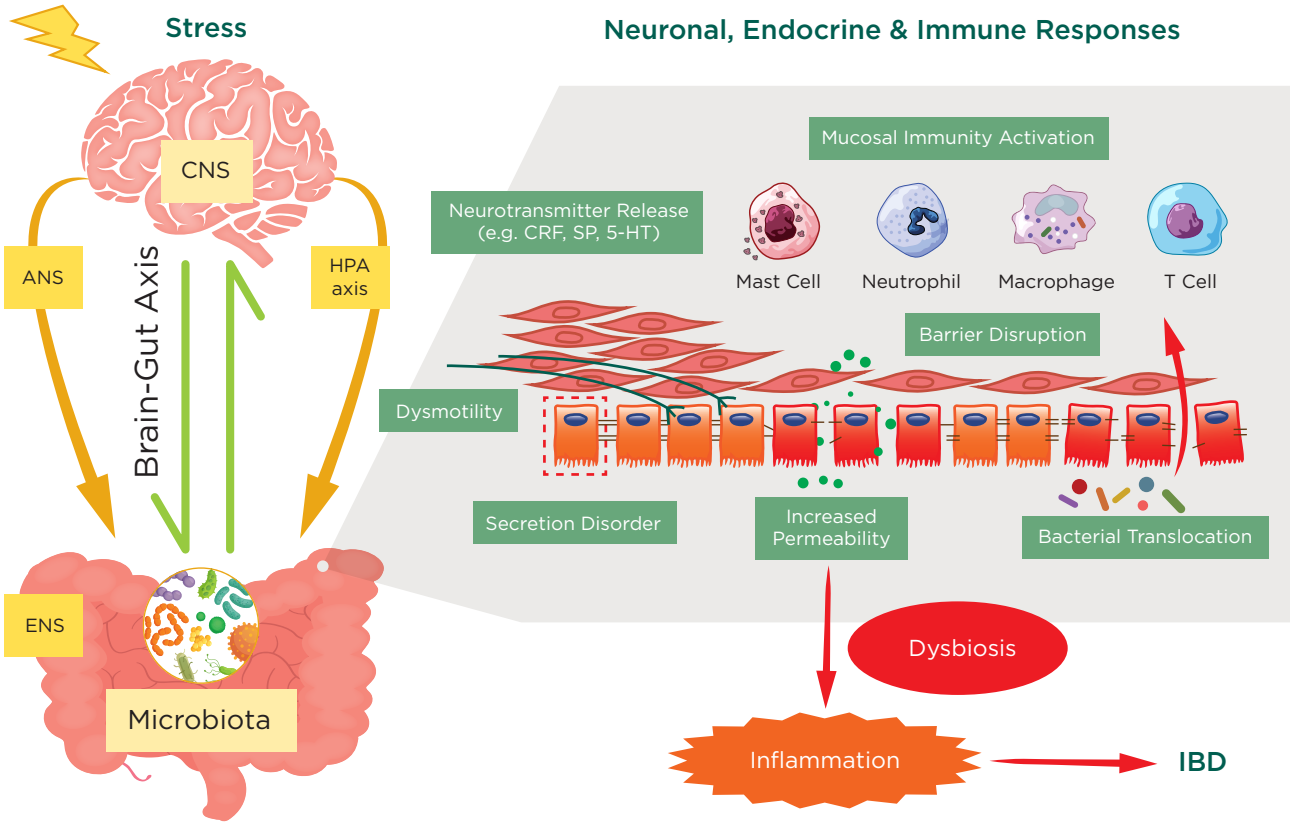
- **Defective innate immune response and the NOD_2/$CARD_{15}$ gene** – The innate immune system responds immediately to pathogens that enter the GIT by activating macrophages and natural killer (NK) cells.[16] Genome-wide scanning has identified the NOD_2/$CARD_{15}$ gene is associated with CD.[1] Patients carrying this gene have an increased innate immune response to commensal organisms as demonstrated by mucosal and serum antibodies, such as anti-*Saccharomyces cerevisiae* antibodies (ASCA).[17] Defects in the NOD_2 gene lead to increased activation of nuclear transcription factor-kappa B cells (NFkB), IL-1β and IL-8, which are key inducers of inflammation in CD.[18] Additionally, the highest quantities of $CARD_{15}$ mRNA are found in the Paneth cells of the small intestine, which synthesise and release antibacterial proteins such as defensin, commonly depleted in CD.[19]
- **Adherent invasive *E.coli* (AIEC) and *Mycobacterium avium* spp. *paratuberculosis* (MAP) infections** – AIEC is thought to play a role in the aetiology of CD and has been reported in several independent studies.[20] AIEC bacteria can survive and replicate extensively within macrophages, stimulating intestinal inflammation via TNF-α.[21] While other research shows AIEC bacteria can target M cells, allowing them to translocate across the intestinal epithelial barrier,[22] moving deep into intestinal tissue, promoting inflammation.[23] Further, defects in autophagy linked to mutations in ATG16L1, IRGM and NOD_2 genes (which are involved in the recognition and elimination of intracellular bacteria), favour AIEC replication within epithelial cells and dendritic cells.[21]

  The role of *Mycobacterium avium* spp. *paratuberculosis* in the role of CD remains controversial, however, it is postulated that the loss of immune tolerance is an effector cytokine response to re-exposure of MAP.[24] The Hruska Postulate, proposes CD is the interaction of two immune responses to MAP involving an immature immune system that has been sensitised to MPA, with later exposure triggering a chronic immune response.[25]

Risk Factors

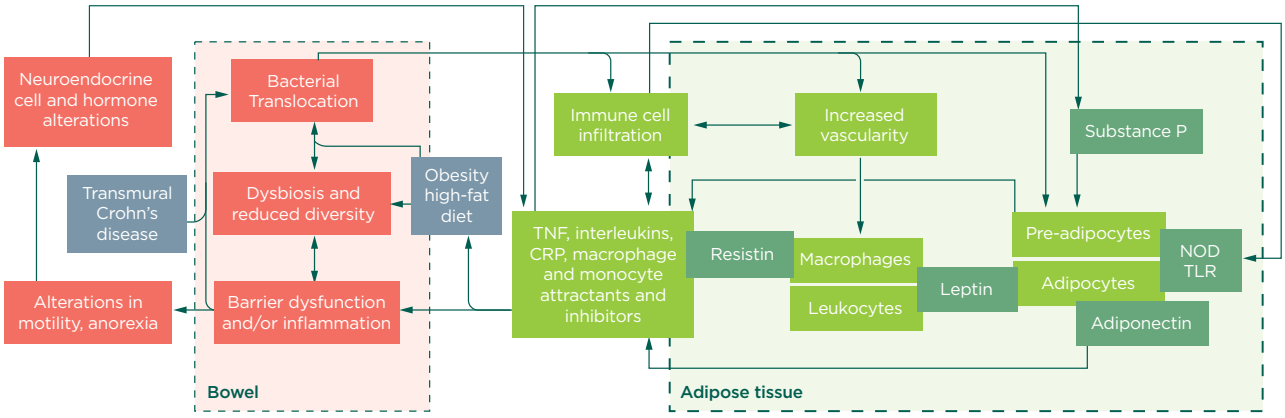
- **Smoking** – UC is more common in non-smokers and ex-smokers, however is not significantly associated with negative outcomes.[26] CD is more common in smokers and is associated with an increased risk of corticosteroid-dependence, surgery and disease progression.[26]
- **Diet** – UC is associated with a diet high in *trans*-fats, omega-6 fatty acids and meat, while CD is associated with a low-residue, high-refined sugar diet.[1]
- **Stress** – Increasing evidence from clinical and experimental studies suggests that stress influences both the development and exacerbation of IBD, due to its ability to increase intestinal permeability, alter immune function and increase intestinal inflammation (see Figure 1).[27,28]
- **Obesity** – Studies have shown 15% to 40% of patients with IBD are obese, despite many IBD patient's being malnourished. The increased risk of IBD in obese patients is thought to be due to the pro-inflammatory environment created by excess adipose tissue. Obesity, a high fat diet and intestinal inflammation result in impaired mucosal barrier, altering tight-junction proteins, promoting bacterial translocation (see Figure 2).[29]
- **Infections** – UC is associated with CMV[14], while CD is associated with AIEC[21] and potentially MAP.[25]
- **Endocrine disrupting chemicals (EDCs)** – EDC's may increase the risk of CD as observational studies have found that bisphenol A (BPA) significantly increased systemic inflammation in CD patients with gut barrier dysfunction.[30]
- **Medications** – IBD is generally associated with repeated antibiotic use, due to their effect on intestinal microbiota.[31] UC has a stronger association with cyclosporin (increased risk of infection) and non-steroidal anti-inflammatory (NSAIDs) (increased epithelial damage), while the oral contraceptive pill (OCP) has a stronger association in CD than UC.[1]

Figure 1 | The impact of stress neuronal, endocrine and immune responses in IBD.[28]



CNS, central nervous system; CRF, corticotrophin releasing factor; SP, substance P; 5-HT, 5-hydroxytryptamine. HPA axis, hypothalamic-pituitary-adrenal axis; ANS, autonomic nervous system; ENS, enteric nervous system.

Figure 2 | Pathogenesis and feedback loop between visceral adipose tissue and intestinal inflammation in IBD.[29]



TNF, tumour necrosis factor; CRP, C-reactive protein, NOD, nucleotide-binding oligomerisation domain-like receptors; TLR, toll-like receptor

Signs and Symptoms[1,3]

Signs/Symptoms	IBD	UC	CD
Urgency		+	
Diarrhoea	++		
Rectal bleeding	++		
Rectal mucous		+	
Abdominal pain	++		
Weight loss	++		
Anorexia	++		
Fever	++		
Nausea		+	
Vomiting		+	
Proctitis (UC in the rectum only) may present with constipation		+	
Perianal fissures and abscesses			+
Constipation			+
Fatigue			+

Alarm signs

The presence of fever, anorexia and weight loss indicate the risk of life-threatening complications such as toxic megacolon, perforation or haemorrhage.[3] Refer the patient to their General Practitioner or local Emergency Department immediately for further investigation.

Differential Diagnosis[1,3]

CD	UC
• Infectious diarrhoea (*Campylobactor*, *Salmonella*, *Shingella*, *Clostridium difficile*, *Entamoeba histolyica*) • CMV, *Schistosomiasis*, *Chlamydia herpes simplex* • Bowel cancer • Ischemic colitis	• Appendicitis/ appendiceal abscess • Cancer (caecal or ileal adenocarcinoma, lymphoma, metastatic cancer, carcinoid tumour) • Infection (*Salmonella*, *Yersinia* spp., *Mycobacterium tuberculosis*, AIEC, MAP • Vascular disorders • Gynaecological disorders

Diagnosis and Tests[3]

- pANCA and ASCA
- Full blood count (FBC) – haemoglobin, white cell count, creatine, albumin
- Erythrocyte sedimentation rate (ESR)
- C-reactive protein (CRP)
- Electrolyte/liver function test (e/LFT) – electrolytes
- Full iron studies
- Holotranscobalamin (Holo TC - active B12)
- Folate
- Vitamin D – particularly in CD
- Stool culture
- Sigmoidoscopy/colonoscopy
- Radiography
- Bone density should be tested at 1 to 2-year intervals for those who have received corticosteroids at high doses for long durations
- Lactulose/mannitol test
- Microbiome testing

Complications

Intestinal inflammation can lead to secondary complications including:

- **Malnutrition and weight loss** – are common in IBD patients due to anorexia, malabsorption secondary to intestinal inflammation, diarrhoea, vomiting, and increased nutrient requirements, as a consequence of chronic inflammation.[3] Studies have shown the following nutrients are often deficient in UC patients:
  - Beta carotene[32]
  - Vitamin C[32]
  - Magnesium[33]
  - Selenium[33]
  - Zinc[33]
  - Iron[34]
  - Vitamin D[34]
  - Vitamin B12[34]
  - Folate[34]

Further, weight and body mass are often lower in UC patients.[3]

- **Osteoporosis** – Chronic inflammation results in a reduction in bone mineral density (BMD), leading to osteopenia and osteoporosis.[35] It is also a consequence of long-term corticosteroid use, which stimulates osteoclastogenesis.[3] Nutritional deficiencies including a lower intake of protein, calcium, phosphorus, vitamins B2, and D further contribute to bone loss.[3,35]
- **Anaemia** – Coexists with IBD in up to two-thirds of patients, commonly presenting with either iron deficiency anaemia (IDA) or anaemia of chronic disease (ACD), which often overlap. IDA occurs in IBD patients due to chronic blood loss due to mucosal ulceration and impaired iron absorption, as a result of inflamed mucosal surfaces.[36] ACD is a consequence of ongoing inflammation (particularly IL-1, TNF-α, INF-γ, and IL-6) and involves iron sequestration, impaired proliferation and maturation of red blood cell (RBC) progenitors, and reduced life span of RBC.[36] In ACD, inflammation increases hepcidin levels, which binds to ferroportin, the transmembrane protein that exports iron into the plasma (present on intestinal epithelial cells and macrophages). Binding of hepcidin to ferroportin results in iron being trapped inside the cell and unavailable for RBC production.[36] As such, supplementation with iron may not always be appropriate. ACD may be suspected if patients have microcytic or normocytic anaemia and a serum ferritin level of < 100 ng/mL (< 224.7 pmol/L) in a patient with inflammation, as serum ferritin is usually elevated as an acute-phase reactant.[37]

Complications of commonly prescribed medications:

- **NSAIDs** - Are toxic to the intestinal epithelium and long-term use may cause erosions, perforations, and ulcers in the gut.[38]
- **Sulfasalazine and methotrexate** - Inhibit the absorption and metabolism of folic acid and may cause folic acid deficiency, potentially resulting in serious blood disorders and the possibility of harming the foetus during pregnancy.[39]
- **Corticosteroids** - Side effects include, weight gain, increased risk of diabetes, osteoporosis, cataract formation, peptic ulcer disease (especially when used in combination with NSAIDs), and avascular necrosis.[40]
- **Immunosuppressant medications** - Are associated with significant side effects, including influenza-like syndrome with myalgia, nausea and vomiting, leucopenia, hepatotoxicity, and pancreatitis. These pharmaceuticals are also associated with a two-to-three-fold increase in lymphoma.[1]
- **Anti-TNF antibodies** - Associated with an increased risk of infections and possibly of malignancy.[1]

Associated Systems and Factors[41]

More than a third of patients with IBD are affected by extraintestinal complications, the most common of which include:

- Spondyloarthritis (SpA) and other arthropathies
- Osteoporosis (particularly in those who have been on long-term corticosteroid therapy)
- Mucocutaneous and ophthalmological manifestations (e.g. anterior uveitis and episcleritis)
- Skin diseases (e.g. pyoderma gangrenosum and erythema nodosum)
- Conditions affecting the hepatobiliary system (e.g. primary sclerosing cholangitis)

Herbal Medicine

Inflammatory Bowel Disease (IBD)	
Therapeutic Goals	**Herbal Medicine**
Reduce intestinal inflammation	Boswellia, turmeric, ginger, licorice, golden seal, chamomile, feverfew
Protect bowel mucosa	Acacia gum, partially hydrolysed guar gum (PHGG), slippery elm, marshmallow, licorice
Improve antioxidant status	Green tea, turmeric, grape seed, rosemary, St Mary's thistle
Address symptoms (diarrhoea, rectal bleeding, pain, fatigue, anorexia)	Chamomile, cinnamon, peppermint, ginger, raspberry leaf, yarrow
Address stress/anxiety	Passionflower, chamomile, St John's wort, lavender, vervain, skullcap, rhodiola, kava, withania, tinospora, rehmannia, lemon balm

	Ulcerative Colitis (UC)	**Crohn's Disease (CD)**
Therapeutic Goals	**Herbal Medicine**	
Improve barrier integrity	Focus on mucoprotection Licorice, slippery elm, golden seal, lecithin	Focus on gut wall healing Licorice, meadowsweet, chamomile, golden seal, gotu kola, slippery elm
Address stealth pathogens	Improve antiviral clearance Sweet wormwood, St John's wort, thuja	Correct dysbiosis Myrrh, phellodendron, andrographis, anise oil, oregano oil, thyme, sage, garlic, golden seal, barberry, propolis
Balance immune function	Modulate immune response Echinacea, andrographis, tinospora, hemidesmus	Improve innate immune response Echinacea, astragalus

Echinacea

- Immune modulator and anti-inflammatory,[42] indicated for autoimmune conditions.
- In resting cells exposed to echinacea, immune status is increased to allow a faster immune response to occur when exposed to a threat (immune 'primer'). When cells are over-stimulated, exposure to echinacea reduces the magnitude of the immune response.[43]
- Modulates the immune response via:
  - Macrophage and T cell responses;[43,44]
  - Increased expression of heat shock protein 70 (Hsp70);[45] and
  - Binding of alkylamindes to cannabinoid 2 (CD2) receptors of the endocannabinoid system (ECS).[46]

Turmeric

- Is a potent anti-inflammatory and antioxidant, as well as an antimicrobial and carminative.[42]
- Exerts potent anti-inflammatory activity via inhibition of NFkB, cyclooxygenase 2 (COX2), 5-lipoxygenase (5-LOX), TNF-α, IL-1, IL-6, and inducible nitric oxide (iNOS).[47]
- Curcumin has been shown to inhibit INF-γ signalling in colonocytes, a pro-inflammatory cytokine that affects the intestinal epithelium by disrupting the epithelial barrier function; preventing epithelial cell migration and wound healing.[48]
- A randomised, multicentre, double-blind, placebo-controlled trial found turmeric, in combination with standard medication, was more effective in maintaining remission than medication alone in IBD patients.[49]
- A pilot study found curcumin improved ulcerative proctitis, leading to reductions in medication.[50]

Boswellia

- Potent anti-inflammatory shown to inhibit 5-LOX and TNF-α.[51]
- Studies have demonstrated boswellia to be as effective, if not more effective, than medication in the treatment of IBD.
- A double-blind clinical trial (n=102) randomised patients with active CD to receive either boswellia or mesalamine. The boswellia extract was shown to be as effective as mesalamine in reducing Crohn's Disease Activity Index (CDAI).[52]
- In a small clinical study of 30 patients with UC, 900 mg/day of boswellia extract taken for six weeks was shown to be more effective and have fewer side effects than sulfasalazine, with comparable improvements in stool properties, histopathology and serum chemistry.[53]

Andrographis

- Anti-inflammatory and potent immune herb.[42]
- Shown to inhibit TNF-α, IL-1 and NFkB *in vivo*.[3]
- In a randomised, double-blind, placebo-controlled study of 244 patients with mild to moderate UC, andrographis was shown to improve clinical symptoms.[54]

Nutritional Medicine

*Assess specific nutrient deficiencies outlined below, particularly iron, vitamin B12, folate, and vitamin D; supplement if indicated. Due to widespread nutritional deficiencies in these patients, a multivitamin is recommended to cover their increased nutritional requirements.

Therapeutic Goals	Nutritional Medicine
Inflammatory Bowel Disease (IBD)	
Reduce intestinal inflammation	N-acetylcysteine (NAC), palmitoylethanolamide (PEA), omega-3 fatty acids, glutamine, zinc, bioflavonoids, vitamin D, bromelain
Protect bowel mucosa	Zinc, glutamine, prebiotics (*see diet section below*), probiotics (*Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24, *Lactococcus lactis* W19, *Lactococcus Lactis* W58)
Improve antioxidant status	Beta carotene, vitamins A, C and E, zinc, selenium, glutathione
Address symptoms (diarrhoea, rectal bleeding, pain, fatigue, anorexia, weight loss)	Prebiotics (*see diet section below*), probiotics (*Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24, *Lactococcus lactis* W19, *Lactococcus Lactis* W58), fibre (*see diet section below*), PEA
Address nutrient deficiencies, prevent anaemia and osteoporosis	Beta-carotene, vitamin C, magnesium, selenium, zinc, protein, calcium, phosphorous, vitamin B2, vitamin B12, folate, vitamin D
Address stress/anxiety	Magnesium, B vitamins, vitamin C
Improve barrier integrity	Glutamine, zinc, vitamin A, vitamin C
Address stealth pathogens	Zinc, vitamin C
Balance immune function	Vitamin D, zinc, vitamin A, vitamin C, selenium

Vitamin D

- Deficiency is common in IBD patients, with a prevalence of 10% to 75%.[55]
- Is an anti-inflammatory and immune modulator, which plays important roles in the maintenance of the epithelial barrier and bone mineralisation.[56]
- 5000 IU/day for 24 weeks has been shown to correct a deficiency in CD patients and was associated with a reduced risk of surgery and lower CDAI in mild to moderate disease states.[57]
- Has been shown to reduce markers of inflammation in IBD patients including high-sensitivity CRP (hsCRP), IL-6 and ESR.[58,59]
- Helps to prevent IBD by maintaining the epithelial barrier as it is involved in epithelial cell restitution.[60]

Glutamine

- Is a major fuel source for enterocytes.[61]
- Reduces intestinal permeability in healthy subjects.[62]
- Reduces intestinal inflammation by inducing the expression of cytoprotective heat shock proteins in epithelial cells.[63]
- Activates peroxisome proliferator-activated receptor gamma (PPAR-γ), an endogenous regulator of GI inflammation.[64]
- Combined with probiotics, glutamine reduces intestinal inflammation and oxidative stress, inhibiting NO and reducing inflammatory mediator's TNF-α, IL-6 and IL-8.[65]
- Has been shown to be beneficial in treating post-operative pouchitis.[61]

Zinc

- Is a common deficiency in IBD patients with a prevalence of 15% to 40% during disease and remission,[66,67] which contributes to mucosal inflammation in IBD patients.[68]
- Is essential for the first step in epithelial wound healing (epithelial cell restitution),[69] with zinc-deficient epithelial cells showing a decreased expression of zonula occludens-1 (ZO-1) and occulin.[70]
- Promotes tight junction organisation and function by regulating TNF-α, IL-1β and NFkB.[71]
- Patients with CD have demonstrated improvement in mucosal permeability with zinc supplementation.[72]

Omega-3 fatty acids

- May help to reduce mucosal inflammation in IBD due to their potent anti-inflammatory effects.
- Higher intake of omega-3 fatty acids may reduce the risk of developing UC, with a diet rich in omega-3 fatty acids compared to omega-6 fatty acids found to be associated with a reduction in disease relapse.[73]
- Have been shown to reduce inflammatory mediators in CD.[74]
- A large prospective study involving 229 702 patients found an inverse relationship between intake of docosahexaenoic acid (DHA) and the development of CD.[75]

Dietary Considerations

- **Increase prebiotic and fibre intake**,# both soluble and insoluble, to increase SCFA production, which provide energy for colonocytes, and reduce intestinal inflammation.[76] Include fibres such as psyllium husk, oat bran, and slippery elm. A placebo-controlled trial of UC patients in remission found psyllium husk was associated with 69% improvement in GI symptoms compared to placebo,[77] and to be as effective as mesalazine for the maintenance of remission.[78] Additionally, oat bran has been shown to increase faecal butyrate concentrations by 36% after one month of supplementation.[79]
- **Increase the consumption of antioxidant-rich foods** due to widespread deficiencies and increased oxidative stress, which is high in inflammatory conditions due to the production of large amounts of reactive oxygen species (ROS).[80] Beta carotene and vitamin C have been found to be low in IBD patients,[81] with other studies demonstrating reduced antioxidant capacity in UC patients.[32] As such, increase foods rich in beta carotene, vitamins A, C and E, zinc and selenium.
- **Ensure adequate protein** as many IBD patients restrict their diet (meat and proteins) to reduce symptoms. Protein is essential for hydrochloric acid, digestive enzyme production and to maintain a healthy weight.[3] Fish is an easily digestible source of protein and a rich source of anti-inflammatory omega-3 fatty acids.
- **Ensure adequate hydration** (2 L water/day plus 1 L for every hour of exercise) to ensure the patient does not become dehydrated from diarrhoea, or to correct stool frequency in those suffering from constipation.
- **Promote a low inflammatory, whole food diet** including the consumption of fruit (if it can be tolerated, choose low fructose fruits) and

#Avoid resistant starch in CD.

5 serves of vegetables (3 of which are green leafy vegetables), to ensure adequate nutritional and phytochemical intake, in addition to prebiotic fibre to promote the growth of beneficial bacteria and reduce intestinal inflammation. Encourage the consumption of omega-3 fatty acids including fish, avocado, nuts, seeds and their oils.

- **Include foods high in mucopolysaccharides** including aloe vera juice, oats, slippery elm, okra, and banana to help promote healing of the GIT. Include cabbage in the diet as it is high in glutamine.
- **Avoidance of lactose and fructose/FODMAP**** may be useful to manage symptoms in CD patients. Studies have found a low FODMAP diet may reduce digestive symptoms including abdominal pain, bloating, flatulence, and diarrhoea.[82] A pilot study also found the restriction of short-chain carbohydrates improved symptom control in IBD patients.[83]
- **A gluten-free or low grain diet** may help to reduce symptoms in those patients with sensitivities. If Coeliac disease or gluten sensitives are suspected, follow a gluten-free diet, and assess symptom changes.
- **Avoid pro-inflammatory foods** such as fried foods and dairy, caffeine, alcohol, and carbonated drinks,[84] due gastric irritant effects.
- During an acute flare of symptoms, patients should **eat easily digestible foods** such as soups, soft-cooked vegetables and slow-cooked meals to reduce the 'load' on the digestive system.[3]

Lifestyle Considerations

- **Quit smoking** - cigarette smoking has been associated with an increased risk of developing CD, with a lower associated risk in UC.[85] In CD, smoking has consistently been associated with a more severe disease presentation and adverse outcomes. Smokers are also more likely to have perianal disease and a propensity towards the stricture phenotype.[86]
- **Manage stress and improve resilience** - stressful events and perceived stress can impact disease severity in IBD patients. Case-control studies have suggested major stressful life events lead to an increased risk of developing IBD, while cohort studies have suggested that higher perceived stress in the preceding 3 to 6 months may be associated with an increased risk of symptomatic flares.[87]
- **Improve sleep** - sleep disturbance is prevalent in IBD patients with 47% to 82% reporting disrupted sleep, night-time waking and non-restorative sleep.[88] The relationship between sleep disturbance and IBD is bidirectional, with active disease associated with poor sleep, and poor sleep negatively influencing disease severity.[26] As such, strategies to improve sleep quality should be employed to improve patient outcomes.
- **Increase exercise** - exercise has been shown to improve immunity and reduce pro-inflammatory cytokines[89] and may be associated with a decreased risk of developing IBD, particularly CD.[26] Studies conducted on the benefits of exercise in IBD patients have found it to improve overall fitness, increase bone density, and reduce stress and anxiety.[26] It is recommended patients with IBD maintain an active lifestyle with moderate-intensity endurance and resistance exercise for at least 30 minutes/day, 4 times/week.[26]

Further Resources

- IBD Support Australia: www.ibdsupport.org.au/tools

**Long-term restriction of carbohydrates can negatively impact the GI mucosa and microbiome. If significant improvement is not seen in the initial weeks of the intervention, reintroduce carbohydrates and investigate alternative dietary interventions for symptom management.

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Curcuma longa

Irritable Bowel Syndrome

Contents

Naturopathic Considerations/Therapeutic Goals

- Identify the cause/s and triggering factors of IBS symptoms
- Address patient's symptoms (nausea, flatulence, abdominal distention, visceral pain, stress/anxiety)
- Identify and treat food intolerance and/or allergies
- Improve digestive function including transit time and peristalsis
- Correct dysbiosis and promote the development of a healthy microbiome
- Decrease mucosal permeability
- Decrease mucosal inflammation
- Address neurotransmitter function
- Address stress and improve resilience

Overview

Irritable bowel syndrome (IBS) is a common functional gastrointestinal (GI) disorder characterised by chronic abdominal pain, changes in bowel habits and other symptoms such as bloating, flatulence and stool urgency.[1,2] It has a global prevalence of 11% and occurs more in women, and those under 50 years of age.[3] IBS is commonly diagnosed using the Rome IV criteria, providing, structural and biochemical causes of the patient's symptoms have been excluded.[2] There are several subtypes of IBS, which are classified according to the patient's predominant stool pattern, as per the Bristol Stool Chart:[4]

- **IBS-C (constipation):** Hard or lumpy stools ≥ 25% and loose or watery stools ≤ 25% of bowel movements.
- **IBS-D (diarrhoea):** Loose or watery stool ≥ 25% and hard or lumpy stool ≤ 25% of bowel movements.
- **IBS-M (mixed):** Hard or lumpy stools ≥ 25% and loose or watery stools ≥ 25% of bowel movements.
- **IBS-U (undetermined):** Insufficient abnormality of stool consistency to meet criteria for IBS constipation, diarrhoea or mixed.

Figure 1 | Bristol stool chart[4]

Type 1	Type 2	Type 3	Type 4	Type 5	Type 6	Type 7
						
Seperate hard lumps, like nuts (hard to pass)	Sausage-shaped but lumpy	Like a sausage but with cracks on its surface	Like a sausage or snake, smooth and soft	Soft blobs with clear-cut edges (passed easily)	Fluffy pieces with ragged edges, a mushy stool	Watery, no solid pieces ENTIRELY LIQUID

Aetiology & Pathophysiology

IBS is a chronic relapsing disorder of unknown aetiology and often varies from person to person. There are, however, several mechanisms which are thought to be involved in the pathogenesis of IBS including dysregulation of the gut-brain axis, altered serotonin (5-HT) signalling, visceral hypersensitivity, GI infection/dysbiosis and alteration in gut flora, and/or food hypersensitivities.[2,5]

- **Dysregulation of gut-brain axis** – The gut-brain axis involves bidirectional communication between the digestive system and the brain via the parasympathetic (PSNS), sympathetic (SNS) and enteric nervous systems (ENS).[6] The PSNS regulates digestion and relaxation (rest and digest), while the SNS governs the flight or fight response. As such, stress has a significant impact on GI function. In IBS, stress often leads to over-stimulation of the SNS, disrupting the process of digestion, leading to pain, discomfort and altered bowel motility.[2] Further, IBS patients are commonly found to have increased SNS activity, with down-regulated PSNS activity[7] and significantly more motility reactions to stressors when compared to healthy subjects.[8]
- **Altered serotonin (5-HT) signalling** – 5-HT signalling plays a crucial role in the control of GI motility as it stimulates the ENS to initiate secretion and peristalsis,[9] with plasma 5-HT concentrations shown to be decreased in IBS patients with constipation, and increased in those with diarrhea.[10] Activation of 5-HT_3 receptors increases motility, secretion and sensation, whereas activation of 5-HT_4 receptor activity has both excitatory and inhibitory effects, including increasing motility and secretion, and decreasing visceral hypersensitivity.[9]

- **Psychopathology** – Increased psychological stress is an important pathophysiological mechanism in IBS patients, with increased reports of anxiety, depression and psychosocial distress.[10] Psychological problems have been found to influence the gut-brain axis, increasing corticotropin-releasing hormone (CRH), impacting mood, digestive motility, visceral hypersensitivity, and inflammatory pathways via neuroendocrine and autonomic pathways.[11] Stress in IBS patients has been shown to increase pro-inflammatory interleukins (IL), activating both the hypothalamic-autonomic nervous system and the hypothalamic-pituitary-adrenal axis (HPA), increasing adrenocorticotropic hormone (ACTH) and cortisol levels.[12]
- **Visceral hypersensitivity** – Intestinal hypersensitivity is a key feature of IBS and is due to the stimulation of different receptors of visceral afferent nerve fibres in the gut wall, trigged by ongoing gut distention and bloating.[13] Visceral hypersensitivity may be increased in those where stress is a significant causative factor.[7] Interestingly, *in vivo* research shows IBS patients with reduced 5-HT are more likely to suffer from visceral hypersensitivity.[14]
- **Gastrointestinal infection** – Individuals may develop IBS after a prolonged GI infection, known as post-infectious IBS,[15] a common example of which is giardia.[10] As such, the disruption of commensal flora and mucosal inflammation post-infection has been proposed to contribute to the pathogenesis of IBS. Mechanisms of post-infectious IBS include residual intestinal inflammation, damage to mucosal immunocytes, enterochromaffin and mast cells, enteric nerves, and changes to the GI microbiota.[16]

  Small intestinal bacterial overgrowth (SIBO) may also contribute to the development of IBS, with a similar overlap in the symptomology of IBS-D including abdominal discomfort, diarrhoea and bloating.[17] In one study evaluating the presence of SIBO in IBS patients, 36% tested positive for SIBO via a glucose breath test.[19] Further research supports a positive association in patients with IBS-D and SIBO. These patients were found to have higher levels of *Prevotella*, with the severity of symptoms correlating with the abundance of *Prevotella*.[17]
- **Alteration in gut flora** – Gut flora is often disrupted in IBS patients, evidenced by decreased faecal microbial diversity in IBS patients compared to healthy populations.[10] Further, *Lactobacilli* and *Bifidobacterial* populations have been found to be diminished in IBS patients, with their activities significantly compromised.[15] Abnormal microbiota populations may lead to further opportunistic infections and immune activity that results in increased intestinal permeability, activated nociceptive sensory pathways and further dysregulation of the ENS.[19]
- **Food hypersensitivities** – Food intolerances trigger intestinal inflammation, damage and hyperpermeability to the GI mucosa, this results in a progressive worsening of IBS symptoms. Patients with IBS often report their symptoms are triggered by specific foods, which can vary from patient to patient. Common intolerances associated with IBS symptoms include enzyme deficiencies (e.g. lactose intolerance), fructose intolerance, intolerance to fermentable oligosaccharide, disaccharide, monosaccharide, and polyols (FODMAP), and gluten sensitivities.[2] The removal of lactose, fructose and FODMAPs from the diet often helps with symptom control, particularly in IBS-D patients, due to poor absorption and osmotic effect of these carbohydrates. Restriction of FODMAPs in IBS patients is increasingly being supported by evidence, and while not all patients respond to this intervention, studies report up to an 86% reduction in GI symptoms with this intervention.[2,20]

Risk Factors[5]

- Genetic predisposition
- History of enteric infections
- Medications - antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), oral contraceptive pill (OCP)
- History of stressful life events and/or
- Current anxiety or depressive disorders

Signs and Symptoms[2,5]

- Abdominal cramping
- Altered bowel motions
- Stool urgency
- Incomplete evacuation
- Abdominal distention
- Abdominal/visceral pain
- Passage of mucous in the stool
- Bloating
- Flatulence
- Nausea
- Fatigue
- Back pain

Alarm Signs[10,21]

- Change in bowel habit to looser or continuous stools for over 6 weeks
- Blood in the stool – refer to a General Practitioner for investigation
- Rectal masses
- Abdominal masses
- Anaemia
- Raised inflammatory markers
- Fever
- Weight loss
- Family history of bowel or ovarian cancer

Diagnosis and Tests[2,4,5,22]

The diagnosis of IBS is one of exclusion, with no accepted biological marker that can be used to diagnose IBS. As such, a symptom-based diagnostic criterion has been developed to diagnose IBS; the Rome IV criteria, which has been updated from Rome III.

Rome IV Diagnostic Criteria for IBS

Recurrent abdominal pain, on average, at least 1 day/week in the last 3 months, associated with two or more of the following criteria:

- Related to defecation
- Associated with a change in frequency of stool
- Associated with a change in form (appearance of stool)
- Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

An important difference between Rome IV and Rome III criteria is that IBS subtypes are based on the patient's reported bowel habits on days with abnormal bowel movements, and not an average of all days, which may include days with normal bowel habits.

Other common investigations that do not specifically relate to diagnosis include:[2]

- Full blood count (FBC)
- Erythrocyte sedimentation rate (ESR)
- C-reactive protein (CRP)
- Electrolyte/liver function test (e/LFT)
- Full iron studies
- Holotranscobalamin (Holo TC - active B12)
- Coeliac serology and genotyping
- IgG radioallergosorbent test (RAST)
- Breath tests (to identify lactose/fructose malabsorption or SIBO)
- Lactose/mannitol test (to identify intestinal permeability)
- Stool analysis
- Microbiome testing
- Colonoscopy

Differential Diagnosis

As IBS symptoms overlap with other GI disorders, it is important to consider, test for, and exclude the following conditions:[5,21]

- Lactose/sorbitol/fructose intolerance
- FODMAP sensitivity
- Coeliac disease/gluten sensitivity
- Excess alcohol/caffeine
- SIBO
- Parasitic infection (*Giardia* spp., *Blastocystis* spp., etc.)
- Inflammatory bowel disease (IBD)
- Post-cholecystectomy syndrome
- Drug induced diarrhoea
- Laxative abuse
- Eosinophilic gastritis or enteritis
- Microscopic colitis
- Bile acid diarrhoea

Associated Systems and Factors[10]

- Other functional gastrointestinal disorders (FGIDs)
- Fibromyalgia
- Chronic fatigue syndrome
- Temporomandibular joint tissue
- Chronic pelvic pain
- Depression
- Anxiety

Herbal Medicine

Therapeutic Goals	Herbal Medicine
Address symptoms (nausea, flatulence, abdominal distention, visceral pain)	Ginger, chamomile, peppermint, lemon balm, fennel, lavender, rosemary, turmeric
Improve digestive function including transit time and peristalsis	Digestive stimulant* - ginger
	Diarrhoea - raspberry leaf, cinnamon, pomegranate, chamomile, slippery elm, green tea
	Constipation - rehmannia, licorice, partially hydrolysed guar gum, slippery elm, barberry, gentian
	Spasmolytic - chamomile, peppermint, fennel, ginger, lemon balm, corydalis, cramp bark
	Choleretic - globe artichoke, barberry, golden seal, greater celandine, St. Mary's thistle, fringe tree, dandelion root, turmeric
Correct dysbiosis and promote the development of a healthy microbiome	Correct dysbiosis - golden seal, barberry, phellodendron, thyme, myrrh, garlic, pomegranate, propolis
	Promote a healthy microbiome - slippery elm, cacao, red dragon fruit, PHGG, medicinal mushrooms (reishi, shiitake, maitake)
Decrease mucosal permeability	Golden seal, licorice, marshmallow, slippery elm, myrrh, calendula, chamomile, cinnamon
Decrease mucosal inflammation	Boswellia, turmeric, licorice, chamomile, marshmallow, golden seal, meadowsweet
Address neurotransmitter function	St. John's wort, lavender, passionflower, kava
Address stress and improve resilience	Nervines/anxiolytic - passionflower, chamomile, valerian, hops, rosemary, lemon balm, oats green/seed, lavender, kava, skullcap, vervain
	Adaptogens - withania, Siberian ginseng, schisandra, tinospora, rhodiola, gynostemma

*Note, only gentle digestive stimulants should be used initially due to the potential of mucosal irritation in IBS patients. Stronger bitters such as gentian may be considered after initial treatment of mucosal inflammation and permeability.

Peppermint

- Traditionally prescribed for digestive problems, exerting spasmolytic, carminative, cholagogue, and antimicrobial actions.[23]
- Studies supporting the benefits of peppermint in IBS have predominately investigated the essential oil, a key constituent of peppermint. Peppermint oil may be used for short-term use and symptomatic management; however, peppermint tincture may be safer for long-term use as it is a whole plant extract and essential oils can be irritating the mucosa with long-term use.[2]
- One trial involving 72 IBS-D and IBS-M patients investigated the use of enteric-coated oil, finding a total of 40% reduction in total IBS symptoms from baseline including abdominal discomfort, bloating, pain at defecation, and urgency.[24]
- In a randomised, double-blind, placebo-controlled trial peppermint demonstrated significant symptom improvement ($p<0.0001$), compared to placebo after 2 months.[25]
- Other studies have consistently reported significant reductions in IBS symptoms within 3 to 4 weeks,[26] predominately reducing symptoms of abdominal pain and visceral hypersensitivity.

Globe artichoke

- Indicated for IBS due to its ability to reduce constipation, abdominal pain and flatulence.[23]
- Bitter tonic and cholagogue.[23]
- In a study evaluating globe artichoke in dyspepsia, a sub-group of 279 IBS patients demonstrated a reduction in abdominal pain, cramping, bloating, flatulence, and constipation associated with IBS, 6 weeks after treatment. At the end of the study, 96% of participants rated globe artichoke as better than any other treatment they tried for IBS.[27]

Turmeric

- Turmeric is a potent anti-inflammatory, as well as choleretic, antimicrobial and carminative.[23]
- In a partially blinded, randomised pilot study (n=207), 72 mg/day and 144 mg/day of a standardised extract of turmeric taken for 8 weeks, was found to reduced IBS symptoms by 41% and 57%, respectively.[28]
- A 2018 meta-analysis concluded turmeric to be a useful tool in the management of IBS due to its anti-inflammatory properties and ability to modulate the gut microbiota.[29]

St John's wort

- Antidepressant and nervine actions.[23]
- Used in the management of mood disorders including anxiety and depression, it may be considered for IBS patients where symptoms are worse for stress, and to support 5-HT levels.[2]
- Women with IBS treated with a St John's wort extract for 8 weeks were found to have less autonomic nervous system reactivity to stress, as well as significantly improved GI symptoms.[30]

Nutritional Medicine

Therapeutic Goals	Nutritional Medicine
Address symptoms (nausea, flatulence, abdominal distention, visceral pain)	Probiotic strains *Bifidobacterium infantis*, *Lactobacillus plantarum*, *Lactobacillus acidophilus*, *Bifidobacterium lactic*, *Saccharomyces boulardii*
Identify and treat food intolerance and/or allergies	*See diet section below*
Improve digestive function including transit time and peristalsis	Dietary fibre (*see diet section*), digestive enzymes, *Saccharomyces boulardii*
Correct dysbiosis and promote the development of a healthy microbiome	Probiotic strains *Bifidobacterium infantis*, *Lactobacillus plantarum*, *Lactobacillus acidophilus*, *Bifidobacterium lactic*, *Saccharomyces boulardii*
Decrease mucosal permeability	Glutamine, zinc, vitamin A, vitamin E, vitamin C, probiotics
Decrease mucosal inflammation	Glutamine, N-acetylcysteine (NAC), palmitoylethanolamide (PEA), omega-3 fatty acids, bioflavonoids, vitamin D

Zinc carnosine

- Reduces intestinal permeability in healthy subjects.[31]
- Is required for wound healing, supports matrix metalloprotein function and extracellular matrix remodelling.[32]
- Zinc transporter protein deficient animals display defects in connective tissue development.[33]
- IBS has been associated with a copper-zinc imbalance and zinc deficient diet, with replenishment of zinc levels suggested to be protective against IBS development in high-risk individuals.[34]

Glutamine

- Reduces intestinal permeability in healthy subjects.[35]
- Alters colonic bacteria producing a favourable profile including a reduction in Firmicutes:Bacteriodetes ratio in humans.[36]
- In a randomised, placebo-controlled trial evaluating the efficacy of glutamine in the treatment of post-infectious IBS-D over 8 weeks, glutamine was found to dramatically reduce IBS scores, daily bowel frequency, Bristol Stool Scales, and intestinal permeability.[38]
- Glutamine has also been shown to reduce daily bowel movement frequency, improve stool form, and normalise intestinal permeability. Glutamine alleviated IL-13 barrier dysfunction by increasing claudin-1 expression via disruption of the phosphatidylinositol-3-kinase/AKT signalling pathway.[39]

Vitamin D

- In a randomised, placebo-controlled trial, vitamin D was shown to improve the symptoms and quality of life in IBS patients.[39]
- Vitamin D is a common deficiency amongst IBS patients.[40]
- An inverse association has been found between serum vitamin D levels and symptom severity in IBS patients.[41]
- It is thought to exert positive benefits in IBS due to the presence of vitamin D receptors (VDRs) in the gut, affecting gut function, motility and IBS symptoms.[42]

Dietary Considerations

- **A low FODMAP diet** may provide up to 86% symptom reduction, particularly in those with IBS-D.[2] It should be noted, long-term restriction of carbohydrates can negatively impact the GI mucosa and microbiome. If significant improvement is not seen in the initial weeks of the intervention, reintroduce carbohydrates into the patient's diet and investigate alternative dietary interventions for symptom management. In IBS-D particularly, avoidance of lactose, sorbitol, fructose, and FODMAPS appear to result in greater symptom reduction.
- **A gluten-free or low grain diet** may help to reduce symptoms in those patients with sensitivities. If Coeliac disease or gluten sensitives are suspected, follow a gluten-free diet, and assess symptom changes.
- **The elimination diet** may be of use to identify foods that trigger symptoms in IBS patients. Identify foods and beverages that trigger symptoms and advise the patient to avoid these foods for 6 to 8 weeks. After this period begin the process of reintroduction and evaluate the patient's response. Advise the patient to avoid foods they consistently react to.
- **Increase fibre intake**†, both soluble and insoluble, to help regulate bowel motility, particularly in IBS-C. Fibre also helps to promote beneficial microbial changes, increase SCFA production, improve mucosal integrity, and reduce inflammation in the gut.[5] Include fibres such as slippery elm, PHGG, psyllium husk, and flax meal. For IBS-C, PHGG is particularly useful to reduce chronic constipation (within 4 weeks),[43] support beneficial flora and increase SCFA production,[44] and suppress the growth of pathogens, specifically in SIBO.[45]
- **Ensure adequate protein**, as many IBS patients restrict meat and proteins to reduce symptoms. Protein is essential for hydrochloric acid and digestive enzyme production, as well as neurotransmitter synthesis.[2] Fish is an easily digestible source of protein and a rich source of anti-inflammatory omega-3 fatty acids, which are also essential for neurotransmitter synthesis.
- **Encourage adequate hydration** (2 L water/day plus 1 L for every hour of exercise) to ensure the patient does not become dehydrated from diarrhoea, or to correct stool frequency in those suffering from constipation.
- **Promote a low inflammatory**, whole food diet including the consumption of fruit (if it can be tolerated, choose low fructose fruits) and 5 serves of vegetables (3 of which are green leafy vegetables), to ensure adequate phytochemical intake and prebiotic fibre to promote the growth of beneficial bacteria.
- **Reduce caffeine, alcohol and carbonated drinks**,[10] due to their pro-inflammatory and irritant effects.

† Fibre may exacerbate symptoms in IBS patients. As such, introduce small amounts of fibre slowly, and gradually increase.

Lifestyle Considerations

- **Exercise** has been shown to improve GI symptoms of IBS, in addition to reducing stress, which has a positive effect on IBS symptomology.[46] In a randomised, controlled study, exercise reduced constipation within 12 weeks.[47] While another study demonstrated exercise reduces gas retention, when compared to rest ($p<0.05$).[48]
- **Stress is a well-known trigger** of IBS symptoms and directly relates to symptom severity. IBS is independently associated with work stress, anxiety, and sleep disturbances.[49] As such, in those patients where stress is a contributing factor, strategies to reduce stress should be encouraged. Where appropriate, refer patients for counselling.
- **Mind-body therapies** such as yoga, tai chi, mediation, deep-breathing exercises, and relaxation techniques have all shown benefits in IBS symptom reduction.[26] Specifically, yoga has been shown to reduce anxiety levels and reduce GI symptoms in IBS patients.[50]
- **Cognitive behavioural therapy** has shown promise in the treatment of IBS, with studies demonstrating improved psychosocial functioning, improved stress management and relief of IBS symptoms including visceral hypersensitivity, pain, bloating, and diarrhoea.[51]
- **Hypnotherapy** may also be useful in managing IBS, with several studies demonstrating long-lasting efficacy of gut-related hypnotherapy.[52] A systematic review found gut-directed hypnotherapy was superior to standard medical treatment in children with IBS.[52]

Further Resources

- Low FODMAP Diet Monash University: https://www.monashfodmap.com/ibs-central/i-have-ibs/starting-the-low-fodmap-diet/

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Matricia chamomilla

Peptic Ulcer Disease

Contents

Naturopathic Considerations/Therapeutic Goals

- Determine cause – testing for *Helicobacter pylori* (*H. pylori*) infection is recommended, case history including non-steroidal anti-inflammatory (NSAID) use, cigarette smoking and stress levels
- If *H. pylori* is detected:
  - Inhibit bacterial growth
  - Eradicate infection in oral cavity reservoirs
  - Reduce adherence
  - Reduce biotoxins
  - Disrupt biofilm
- Repair the gastrointestinal mucosa and promote ulcer healing
- Relieve inflammation and pain
- Improve antioxidant status
- Support gastrointestinal microcirculation
- Address stress if indicated
- Address contributing lifestyle factors e.g. smoking

Overview

Peptic ulcer disease (PUD) generally affects the stomach or the first few centimetres of the duodenum. It involves a lesion that penetrates a segement of the muscularis mucosae in these areas. Ulcer size can range between several millimetres to several centimetres. While they most commonly affect middle-aged adults, infants and children may experience them too.[1]

Aetiology & Pathophysiology

Ulcers arise due to an imbalance between ulcerogenic (hostile) factors and protective factors, which causes acid erosion of the mucosa, sub-mucosa and muscular layers.[2,3] In health, the gastric and duodenal mucosa is protected by bicarbonate secretion into the mucous layer, neutralising pH at the epithelium, and creating a physical barrier to gastric acid and pepsin.[4] When the mucosal defences are impacted by infection or damaged due to medication use, protection is lost, exposing the gastric epithelium to gastric acid.[3] This process can be potentiated by factors such as alcohol or smoking.[3]

Peptic ulcer development can occur through the following:

- ***H. pylori* infection** – Infection is usually acquired in childhood[2] and is found in the oral cavity, stomach and duodenum[5]. Certain strains of *H. pylori* are more virulent than others and host immune status also affects infection rate.[6] Infection is apparent in about 50% of the population, but only leads to ulceration in 10% to 20% of those infected.[3] Infection is present in 80% of gastric ulcer and 90% of duodenal ulcer cases.[7]

  To adhere to the gut lining, *H. pylori* must survive very low gastric pH, penetrate the mucous layer and avoid immunological attack. As such, it utilises a number of virulence factors to colonise a host and persist in the environment.[8]

Table 1 | Major virulence factors involved in the persistence of *H. pylori*[8]

Virulence Factors	Roles in Persistent Infection
OipA	• Induces pro-inflammatory cytokines • In combination with CagA, causes disruption of cell tight junctions
VacA	• Increases IL8 expression and causes inflammation • Contributes to long-term colonisation • Cell proliferation and elongation • Increases the level of MAPK signaling
CagA	• Stimulates the NF-κB pathway • Induces apoptosis • Induces pro-inflammatory cytokines • Disrupts cell tight junctions • Increases mucosal inflammation
BabA	• Leads to effective cell adherence • Mediates in the effective interaction between *H. pylori* and epithelial cells
DupA	• Induces pro-inflammatory cytokines • Induces apoptosis
GGT	• Contributes to long-term gastric colonisation • Induces immune response tolerance
SabA	• Mediates the effective interaction between *H. pylori* and epithelial cells

MAPK: Mitogen-activated protein kinase; NF-κB: Nuclear factor-κB, *H. pylori: Helicobacter pylori.*

The ability of *H. pylori* to survive gastric acidity relies on its production of urease, which creates a localised buffered zone – called a micro-niche.[8,9] The spiral and flagellated structure of *H. pylori* enables it to penetrate the gastric and duodenal mucosa and adhere to the epithelial cells below.[8] *H. pylori* evades immunological attack by inducing macrophage apoptosis and deactivation of polymorphonuclear neutrophils and monocytes.[8] Once present, *H. pylori* decreases mucin synthesis,[10] and induces inflammation (liberating nutrients for its survival), which generates reactive oxygen species (ROS) and causes tissue injury.[6,8] *H. pylori* biofilm may play a role in its resistance to therapy.[11]

Post-eradication relapses may occur due to extra-gastric reservoirs of *H. pylori*, such as the oral cavity, especially if periodontal disease is present.[5]

- **NSAID and aspirin use** – NSAID and aspirin associated damage to the gastroduodenal mucosa occurs via inhibition of cyclooxygenase-1 and as a result, reduced prostaglandin production. This results in decreased mucosal blood flow and inhibition of mucous production, bicarbonate secretion and cell proliferation.[2,12] Damage to the protective mucous barrier exposes the epithelium to gastric acid and enzymes causing ulceration.[13]

  In addition, NSAIDs delay healing of peptic ulcers through inhibition of angiogenesis, which is required for mucosal blood flow, delivery of nutrients and mucosal healing.[6]

- **Psychological stress** – While this association is still debated, studies have found stress to be independently associated with increased ulcer incidence.[14] Individuals exposed to severe stress such as natural disasters and critically ill patients, have increased ulcer formation. Proposed mechanisms include increased acid production, as well as the impact of hypothalamic-pituitary-adrenal axis activation altered blood flow, cytokine mediated impairment of mucosal defences, and impaired healing.[14]

- **Smoking** – Smoking cigarettes is associated with both the pathogenesis and delay of healing of peptic ulcers. A large population study found that prevalence of PUD in current and past smokers is almost double compared to non-smokers. It has been shown that the smoke and active ingredients of cigarettes can decrease gastrointestinal mucosa blood flow, negatively impact the mucosal immune system, cause cell death of the mucosa, and inhibit cell renewal. In addition, due to the reduction of gastrointestinal mucosa immune system defence and reduced antioxidant status, cigarette smoking increases the risk of *H. pylori* infection.[15,16]

- **Idopathic** – This diagnosis is made when all other potential causes are ruled out, including the above and other less common causes; drugs such as clopidogrel and bisphosphates, infections including cytomegalovirus, herpes simplex (generally in the immunocompromised), *helicobacter heilmani*, Crohn's disease, eosinophilic gastroduodenitis, tumours, Zollinger-Ellison syndrome, systemic mastocytosis or irradiation therapy.[13,17]

  Although the exact aetiology of idiopathic PUD remains unclear, it is likely influenced by an imbalance between ulcerogenic factors (pepsin, acid or toxic substances) and protective factors (bicarbonate, mucin and growth factors), which will vary between patients.[13] It is important to note that mortality rates and rebleeding episodes are much higher for idiopathic peptic ulcer patients than for those with a known cause.[13]

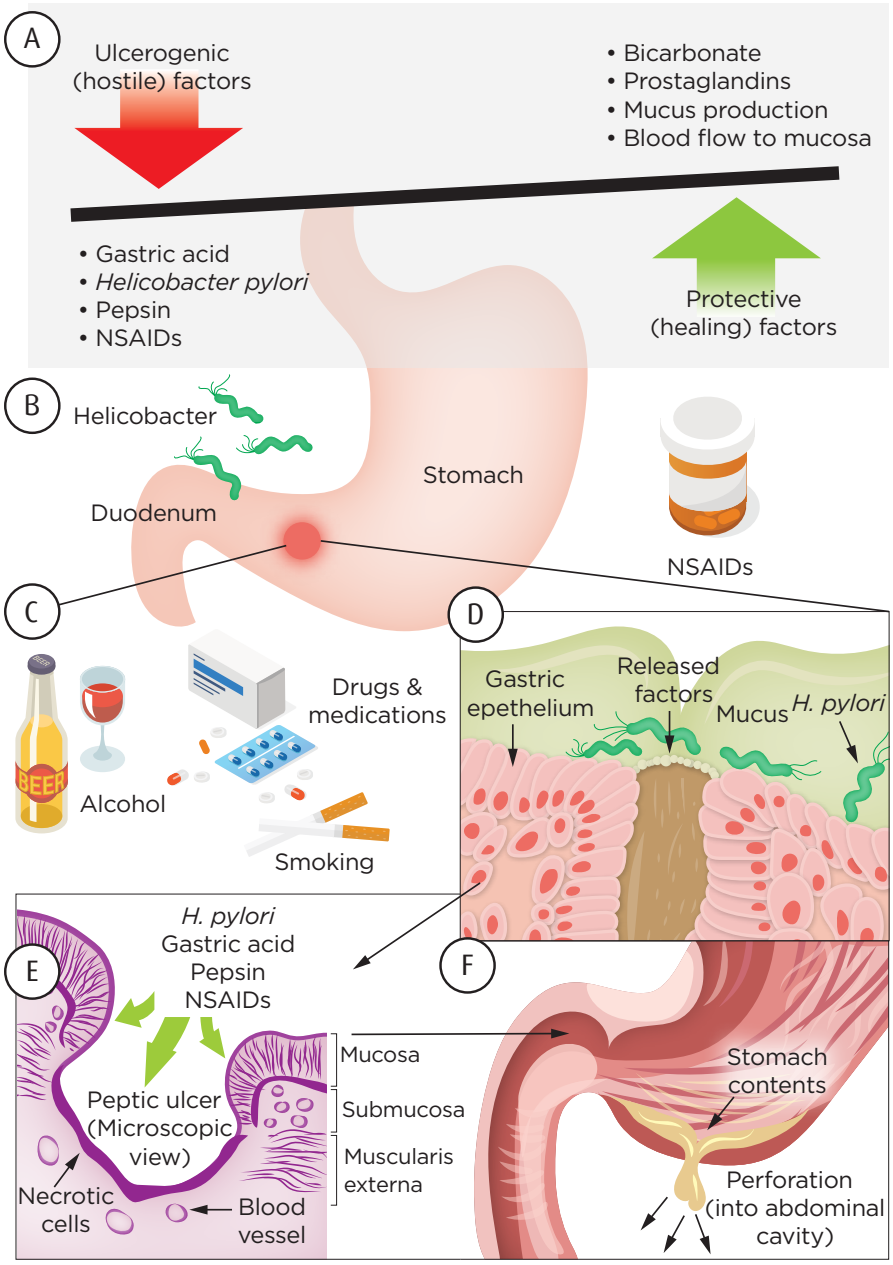
The importance of microcirculation

Vascular insufficiency may play a role in reducing tissue integrity, as adequate blood flow is required by the gastric mucosa to maintain the viability of tissue. While circulation through larger vessels in the stomach is important, protection of mucosa is dependent on optimal microcirculation.[18]

When gastric mucosal blood flow is reduced, hydrogen ions accumulate in the mucosa, a reduction in the neutralising action of bicarbonate occurs and there is reduced removal of toxic waste products, oxygen metabolites and back diffused hydrogen. This results in the mucosa being exposed to hydrogen ions for a prolonged period of time, which causes a decline in pH and damage to cells.[18]

Reduced gastric mucosal blood flow also negatively impacts the maintenance of an unstirred mucus gel layer and prostaglandin secretion, which are protective mechanisms.[18]

Figure 1 | Factors contributing the peptic ulcer development and perforation of ulcer[3]



Risk Factors

"Peptic ulcers are frequently encountered in the primary care setting and understanding associated risk factors is key to disease prevention and management."[2]

- Smoking[15,16]
- Increasing age - The higher risk associated with older people is multifactorial; including high risk medication use e.g. NSAIDs/antiplatelet drugs, long term cigarette smoking, comorbidities and frailty. It is also important to note that older patients experience less abdominal pain related to ulcers.[19]
- NSAID and aspirin use[2,12]
- Stress[12]
- High salt diet[20]
- Clopidogrel and bisphosphates[13]
- Poor general hygiene[11]
- Poor dental hygiene[21]
- Zollinger-Ellison syndrome[12]
- Crohn's disease[12]
- Cocaine use[12]

Signs and Symptoms

- Can be asymptomatic. For those with symptoms, common presentations include:[1,22,23,24]
- Epigastric pain - The pain may be described as gnawing or burning, or as a slow build of hunger pains for 1–2 hours. Pain may be relieved by antacids and may cause awakening at night.

  Gastric ulcer pain – generally aggravated by meals. The patient may avoid food for this reason and report weight loss.

  Duodenal ulcer pain – relieved by meals.
- Indigestion
- Bloating
- Abdominal fullness
- Nausea
- Early satiety
- Belching
- Inability to tolerate fatty foods

Complications

Complications are experienced in approximately 25% of patients. They are more common in the elderly and those taking NSAIDs.[23]

Complications include:[23]

- **Perforation** – 2% to 10% of patients with PUD may experience perforation. This can be a surgical emergency.
- **Penetration** – generally presents with persistent upper abdominal pain that radiates to the back.
- **Upper gastrointestinal bleeding** – the most common cause of death or surgery in patients with PUD, it impacts 15% to 20% of patients. Often occurs in asymptomatic older patients, however, they may present with haematemesis, melena or orthostasis fatigue (anemia related).
- **Gastric outlet obstruction** - occurs in less than 5% to 8% of patients. Generally occurring in those with pyloric channel ulcers or recurrent ulcers. Obstruction can be due to acute inflammation, oedema or spasm, or fibrosis and scarring.
- **Gastric cancer** – it is recommended that nonhealing ulcers are investigated to rule out cancer.

Differential Diagnosis[19,25]

- Gastritis
- Gastroenteritis
- Esophagitis
- Functional dyspepsia
- Gastroesophageal reflux disease
- Gastric cancer
- Pancreatitis
- Biliary colic
- Cholecystitis
- Mesenteric ischemia
- Mesenteric vasculitis

Diagnosis and Tests

Endoscopy is used to diagnose PUD and may be combined with a biopsy to delineate between malignant and benign disease.[1] In some cases biopsy samples are utilised for a rapid urease test or histologic staining to identify *H. pylori*.[26]

The preferred non-invasive tests to determine *H. pylori* infection include the urea breath test and stool antigen assay. Both tests have a similar sensitivity and specificity (> 95%) and can confirm eradication after therapy. It is important to note that false negatives can be possible if the patient has received antibiotic therapy recently or is taking a proton pump inhibitor (PPI). As such, it is recommended that follow up tests are not undertaken until 4 weeks after antibiotic cessation or 1 week after PPI cessation.[26]

Associated Systems and Factors

H. pylori infection is associated with many extra-gastric diseases including:[27]

- Ischemic stroke – associated with virulent strains
- Alzheimer's disease
- Parkinson's disease
- Coronary artery disease and myocardial infarction
- Guillain-Barre syndrome
- Rosacea
- Psoriasis
- Chronic urticaria
- Iron deficiency anaemia
- Vitamin B12 deficiency and elevated homocysteine levels
- Primary immune thrombocytopenia
- Open-angle glaucoma, serous chorioretinitis and blepharitis
- Primary biliary cirrhosis

Herbal Medicine

Therapeutic Goals	Herbal Medicine
If *H. pylori* is detected: • Inhibit bacterial growth • Reduce adherence • Reduce virulence factors (e.g. biotoxins) • Disrupt biofilm • Eradicate infection in oral cavity reservoirs	Inhibit bacterial growth Myrrh, sage, garlic (fresh/allicin containing), nigella, oregano oil, thyme, golden seal, propolis, pomegranate Reduce adherence Bearberry, cranberry Reduce virulence factors Phellodendron, licorice, ginkgo, green tea, high tannin herbs e.g. sage Disrupt biofilm Turmeric (adjunct) Eradicate infection in oral cavity reservoirs (*see oral treatment below*)
Repair the gastrointestinal mucosa and promote ulcer healing	Slippery elm, licorice, golden seal, marshmallow, propolis
Relieve inflammation and pain	Turmeric, boswellia, chamomile, licorice
Improve antioxidant status	Rosemary, ginkgo, grapeseed, turmeric, green tea, pomegranate
Support gastrointestinal microcirculation	Ginkgo, grapeseed
Address stress, if indicated	St. John's wort, passionflower, withania, rhodiola, tinospora, gynostemma, skullcap, chamomile, lemon balm, oats seed/green

3 step oral treatment for *H. pylori*:

1. Ayurvedic oil pulling with 1 tablespoon sesame or coconut oil for 15–20 minutes (spit out oil after this time).
2. Clean teeth.
3. Use herbal mouth rinse: Equal parts propolis, myrrh and calendula; or equal parts echinacea, sage and thyme. Combine 2.5 mL of herbal mix in 25 mL of water and swill around the mouth, tongue and gums for 60 seconds.

Turmeric

- A clinical trial reported that after 4 weeks of treatment with encapsulated whole turmeric powder, 48% of patients had absent ulcers, a further 18 patients had ulcer absence after 8 weeks and another 19 patients were ulcer free at 12 weeks.[28]
- Curcumin has free radical scavenging activity, enhances levels of glutathione peroxidase and catalase, prevents peroxidation of membrane lipids and promotes cellular membrane integrity.[6]
- The healing and gastroprotective activity of curcumin is also attributed to its enhancement of matrix metalloproteinase-2 (MMP-2) expression, which causes remodelling and re-epithelialisation of endothelial tissue.[6]

Licorice

- 56% of participants receiving 150 mg/day deglycyrrhizinised licorice (DGL) for 60 days were found to be *H. pylori* free, compared with 4% in the placebo group.[29]
- Was shown to be as effective as carbenoxolone, cimetidine and ranitidine at healing gastric and duodenal ulcers and symptom reduction.[30,31]
- Improves mucosal blood flow in healthy adults.[31]
- Used in Traditional Western Herbal medicine to reduce irritation of gastric mucosal surfaces and for gastric or duodenal ulcer.[30]
- An *in vivo* study demonstrated prevention of ulcer development, reduction in gastric acid secretion, and gastroprotective effect against aspirin, ibuprofen and ethanol.[30]

Chamomile

- α-bisabolo inhibits gastric ulcer formation *in vivo*.[31]
- Anti-inflammatory, vulnerary, anti-ulcer, carminative, mild sedative.[30]

Slippery elm

- Traditionally used to treat irritation and ulceration of the gastrointestinal tract.[32]
- Contains mucilaginous compounds that soothe irritated mucosa in acute gastritis.[32]

Nigella

- Found to have similar *H. pylori* eradication rate to triple antibiotic therapy when combined with omeprazole at 2g/d for 4 weeks.[33]

Nutritional Medicine

Therapeutic Goals	Nutritional Medicine
If *H. pylori* is detected: • Inhibit bacterial growth • Reduce adherence • Reduce virulence factors (e.g. biotoxins) • Disrupt biofilm • Eradicate infection in oral cavity reservoirs	Reduce adherence *Saccharomyces boulardii* Reduce virulence factors *Saccharomyces boulardii* Vitamin C (inhibits urease)[7] Disrupt biofilm N-acetylcysteine (NAC)
Repair the gastrointestinal mucosa and promote ulcer healing	Zinc carnosine, glutamine, vitamin C, vitamin A
Relieve inflammation and pain	Omega-3 fatty acids, bioflavonoids, NAC
Improve antioxidant status	Vitamin C, vitamin E, bioflavonoids, zinc carnosine, NAC
Support gastrointestinal microcirculation	Glutamine
Address stress, if indicated	Magnesium, B group vitamins

Zinc carnosine

- Improves gastric healing and reduces ulcer formation in human studies.[34]
- Healed aspirin-induced intestinal mucosal damage in an uncontrolled human study.[34]
- Improves *H. pylori* eradication rate when combined with triple therapy compared with triple therapy alone.[35]
- Inhibition of ethanol-induced ulcer formation *in vivo.*[36]
- Reduces aspirin-induced duodenal ulceration in humans[7] and *in vivo.*[34]
- Inhibits pro-inflammatory cytokines, restores gastric mucosa, preserves gastric mucous[37], restores gastric glutathione, and improves cell migration and proliferation (early and late cellular healing activity) *in vitro.*[34]
- Improves intestinal permeability in humans.[34]

NAC

- Found to improve eradication rates when combined with triple therapy, possibly by reducing gastric mucous viscosity allowing antibiotics to more easily permeate and reach the site of infection.[38]
- *In vitro* and *in vivo* studies confirm anti-*H. pylori* activity. In addition, an *in vivo* study showed NAC prevents *H. pylori*-induced gastritis.
- Destabilises biofilm, antioxidant, bactericide.[40]
- Reduces oral biofilm *in vitro.*[41]

Glutamine

- Protects against *H. pylori*-induced gastritis *in vivo.*[42]
- Protects enterocytes, down-regulates pro-inflammatory signalling pathways, regulates tight junction proteins, and protects against cellular stressors and apoptosis.[43]
- Increases expression of intestinal mucin after experimental injury *in vivo.*[44]

Probiotics

- A combination of *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24, *Lactococcus lactis* W19, *Lactococcus Lactis* W58 has been found to improve intestinal barrier function *in vitro.*[45]
- *Lactobacillus* strains including *sakei*, *plantarum*, *rhamnosus,* and *brevis* isolated from fermented foods have been found to have anti-*H. pylori* activity.[46]
- Lactic acid from probiotic bacteria can inhibit drug resistant and drug sensitive *H. pylori* strains and limit urease activity.[47]
- *Lactobacillus casei* improves *H. pylori* eradication rates when combined with triple therapy in children with gastritis.[48]

Dietary Considerations

- **Encourage a low inflammatory, whole food diet** high in fibre, fruits and vegetables and flavonoids.
- **Increase foods in beta carotene/vitamin A**, which may assist in prevention of ulcer development/assist in mucosal healing:[49]
  - Carrots
  - Sweet potato
  - Kale
  - Spinach
  - Collard greens
  - Organ meats
  - Eggs
- **Include raw cabbage juice daily** – promoted healing of peptic ulcers in human study.[50]
- **Eat an apple every day** – apple polyphenols have been found to upregulate gastric mucosal glutathione and, reduce aspirin-induced ulcer *in vivo*.[6] Apple polyphenols also increase mucin production, inhibit *H. pylori* infection and reduce *H. pylori*¬-induced gastritis.[6]
- **Avoid processed food** – additives such as polysorbate-80 and carboxymethylcellulose are known to negatively affect gut mucous.[51]
- **Include healing/stress relieving teas** e.g. licorice/chamomile.
- **Include sulfurophane containing foods**. The antioxidant action of sulfurophane protects the gastrointestinal mucosa from *H. pylori*/NSAID induced damage:[52]
  - Broccoli sprouts
  - Broccoli
  - Brussel sprouts
  - Cabbage
  - Cauliflower
  - Kale
  - Watercress

- **Increase antioxidant rich foods** or foods that stimulate Nrf2:
  - Rosemary
  - Garlic
  - Berries
  - Turmeric
  - Green tea

Diet considerations for *H. pylori*

- **Avoid a high salt diet** – *in vivo* research shows that salt causes direct damage to the gastric mucous, increases *H. pylori* colonisation and virulence and leads to an increased risk of gastric cancer.[20]
- **Avoid a high carbohydrate, high sugar diet** as this is associated with an increased risk of *H. pylori*, whereas a diet high in animal offal, seafood and poultry decreases the risk.[53]
- **Consume kefir daily** - found to improve *H. pylori* eradication rates when combined with antibiotic triple therapy and reduce side-effects to treatment.[54]
- **Consuming > 1 cup of green tea per day per week** is associated with lower *H. pylori* infection.[6]
- **Include cranberry juice** (unsweetened) with a high proanthocyanidin content. Clinical trials support the *H. pylori*-suppressive activity of cranberry juice alone in adults and children, or in conjunction with triple antibiotic therapy.[55,56,57,58] Juice containing 44 mg proanthocyanidin consumed twice daily resulted in a 20% reduction in *H. pylori* infection rate over 8 weeks.[59]

Lifestyle Considerations

- **Encourage good oral hygiene practices** due to the correlation between *H. pylori* in the oral cavity, periodontal disease and gastric reinfection.
- **Avoid smoking** as it is associated with the pathogenesis of peptic ulcer disease and reduced healing.[15,16]
- **Observe general hygiene practices** such as regular hand washing to prevent *H. pylori* infection.[59]
- **Avoid the use of medications known to damage the gastric mucosa** – NSAIDs, corticosteroids and bisphosphonates.[1,12,13]
- **Encourage stress management techniques** e.g. meditation, mindfulness. Promote a healthy psychological approach to life stressors – animal models indicate that perceived control over a stressful situation reduces risk of ulceration.[60]

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Small Intestinal Bacterial Overgrowth

Contents

Naturopathic Considerations/Therapeutic Goals	
• Resolve bacterial overgrowth • Improve digestive function and secretions • Regulate colonic dysmotility • Restore a healthy microbiome • Reduce gastrointestinal inflammation	• Heal gastrointestinal mucosa • Address symptoms (bloating, flatulence, abdominal pain, stool regularity) • Address food intolerance/allergies • Address macro and micronutrient deficiencies

Overview

Small intestinal bacterial overgrowth (SIBO) is defined as an alteration or an increase in the type of bacteria in the small bowel causing gastrointestinal symptoms.[1,2,3] Two types of SIBO have been identified. The first is due to a defective gastric barrier, characterised by Gram-positive bacteria from the upper respiratory tract and oral cavity.[4] The second is known as the coliform type, caused by bacteria typically found in the colon, and includes Gram-negative aerobic and anaerobic species that ferment carbohydrates producing gas.[3] Clinically, SIBO may present as frequent intestinal bloating, flatulence, abdominal distention/pain, steatorrhoea, and diarrhoea.[4]

Aetiology & Pathophysiology

While the pathogenesis of SIBO is multifactorial, it is considered to be primarily caused by a dysfunction in the body's natural antibacterial protective mechanisms, and impaired intestinal clearance.[5] In SIBO bacterial populations in the small bowel exceed 10^3 - 10^6 organisms CFU m/L.[3,6]

- **Gastric Acid Barrier** – Conditions that inhibit or reduce gastric acid secretion contribute to the pathogenesis of SIBO, which represents one of the first lines of defences against intestinal pathogens. Conditions such as pernicious anaemia, *Helicobacter pylori* (*H. pylori*) infection, malnutrition, and aging increase the risk of SIBO.[7] Additionally, long-term use of proton pump inhibitors (PPIs), which cause reduced hydrochloric acid production, is also associated with an increased risk of developing SIBO.[8]
- **Impaired intestinal clearance**[8] – Disturbances in intestinal motility are also considered to contribute to the pathogenesis of SIBO. Mechanisms of dysmotility include an absence of phase III migratory motor complex (MMC) [neuropathy], absence or reduced postprandial response, a diminished amplitude of antral/intestinal phasic activity, or impaired antrodueodenal coordination. In a recent study (n = 150) designed to investigate the role of dysmotility and PPI use in patients with persistent gastrointestinal complaints, 53% of patients with chronic gastrointestinal symptoms presented with dysmotility, 76% of these patients also presented with SIBO. This represents a significant relationship (p=0.0003) between dysmotility and SIBO. Both PPI use and dysmotility were found to be independent risk factors for SIBO.
- **Impaired mucosal immunity** – Patients with SIBO are more likely to have impaired mucosal immunity,[9] which is considered to contribute to the pathogenesis of SIBO, as duodenal and jejunal immunoglobulin A immunocytes are shown to be significantly increased in patients with SIBO.[6]

Risk Factors[1,10,11,12,13,14]

- Increasing age
- Diabetes mellitus
- Scleroderma
- Cirrhosis
- Pancreatic exocrine insufficiency
- Irritable bowel syndrome (IBS)
- Coeliac disease
- Inflammatory bowel disease (IBD)
- Diverticulitis
- Short bowel syndrome
- Steatorrhea
- Narcotic use
- Immunodeficiency syndromes (HIV/AIDS)
- Medications including PPIs, histamine 2-receptor blockers (H2RA's) and levothyroxine
- Neurological conditions (e.g. Parkinson's Disease)
- Hypothyroidism

Signs and Symptoms

Signs and symptoms of SIBO are nonspecific and include:[15]

- Belching
- Intestinal bloating
- Flatulence
- Abdominal distention
- Abdominal pain
- Steatorrhoea
- Diarrhoea

Malabsorption may occur secondary to the above signs and symptoms resulting in:[15]

- Weight loss
- Malnutrition (particularly vitamin B12, vitamin D and iron[3])
- Fatigue
- Loss of muscle mass
- Peripheral oedema
- Osteoporosis

Diagnosis and Tests

Diagnosis of SIBO can be challenging due to the nonspecific nature of symptoms, frequent association with other diseases and the absence of objective diagnostic tests.[5] There are, however, two tests that are currently used for the diagnosis of SIBO; jejunal aspirate culture and breath testing.

- **Jejunal aspirate culture** - Considered the 'gold standard', however, this technique is rarely used in clinical practice due to its invasive nature[6] and controversy regarding the cut-off for diagnosis.[3] This procedure involves an endoscopic sample of coliform bacteria isolated from the proximal jejunum, with diagnosis confirmed if the presence of coliform bacteria is >103 CFU/mL.[3]
- **Breath test** - Breath testing is a non-invasive alternative for diagnosing SIBO. This technique involves fasting overnight and consuming a carbohydrate solution (lactulose or glucose). As fermentation occurs along the small intestine, gases are exhaled in the breath. Breath samples are collected at 15-minute intervals over a 2 to 4-hour period, detecting hydrogen and/or methane, indicating the presence of bacteria in the small intestine.[5]

  Lactulose – Assesses the orocaecal transit time and measures the exhaled amount of hydrogen or methane after the ingestion of 10 g of lactulose liquid. A positive SIBO diagnosis is reached when there is a rise of over 20 parts per million (PPM) of hydrogen in a 20-minute period, within 90 minutes of testing.[16] Higher levels of methane are often found in patients with methane predominant bacterial overgrowth and are five times more likely to have constipation,[17] with severity shown to correlate with methane levels.[18]

  Glucose - Measures proximal ileum bacterial overgrowth and is considered more accurate for diagnosing SIBO compared to lactulose.[19] Patients ingest 50 g glucose, a hydrogen peak of >12ppm is considered a positive result.[7]

  While breath testing is a non-invasive and inexpensive method of diagnosis of SIBO, it has its limitations including:[6]
  - Variable sensitivity and specificity
  - Patients must adhere to strict dietary guidelines to avoid false negatives
  - Results may reflect SIBO, IBS or fructose malabsorption
  - Altered transit times – in patients with rapid transit, lactulose may produce an early peak of hydrogen, which may produce a false positive
  - Hydrogen testing may fail to detect overgrowth of methane producers

Other tests that may be useful to investigate SIBO, malnutrition and inflammation include:[1]

- Stool tests and/or microbiome testing
- Full blood count
- C- reactive protein
- Coeliac serology and genotyping
- Full iron studies
- Holotranscobalamin (Holo TC - active B12)
- Vitamin D

Differential Diagnosis[1,5,10]

- Irritable bowel syndrome (IBS)
- Parasitic infection
- Large bowel bacterial overgrowth
- Endometriosis
- Inflammatory Bowel Disease (IBD)
- Coeliac Disease
- Non-coeliac gluten sensitivity
- Small intestine obstruction
- Hypochlorhydria
- Pancreatic enzyme insufficiency
- Fructose malabsorption
- Lactose intolerance
- Food allergies and/or intolerances
- *H. pylori* infection

Complications

Due to an overgrowth of bacteria, SIBO can lead to secondary complications including:

- **Intestinal inflammation** - Occurs in the gut due to the overgrowth of invasive strains of bacteria in the bowel. Inflammation may result in several epithelial changes including damage to the villi and the brush border, which further stimulates cytokine release and inflammatory mediators. This can lead to functional changes in the surface area for absorption, contributing to malnutrition. Inflammation and damage to the mucosal lining contribute to the classic symptoms seen in SIBO.[11]
- **Malnutrition** – Excess bacteria in the small bowel consume nutrients including carbohydrates and vitamin B12, leading to a calorie deficit and vitamin B12 deficiency. The bacteria also deconjugate bile salts, causing failure of micelle formation and subsequent fat malabsorption, which can lead to deficiencies of fat-soluble vitamins (vitamins A, D, E, and K)[11] and diarrhoea. Further, reduced absorption of fat, protein and carbohydrates leads to subsequent weight loss.[6]
- **Osteopenia** – Chronic malabsorption has long been recognised as a cause of osteopenia. In one study, bone mineral density was measured in patients with SIBO and compared against a reference population. Those with SIBO had significantly lower bone density in the femoral neck ($p<0.01$) and in the lumbar spine ($p<0.05$) compared to the reference population.[20]

Associated Systems and Factors

SIBO is associated with several conditions including:[11]

- Anatomical
  - Enteroenteric fistula
  - Small bowel diverticular
  - Surgically created blind loops
  - Intestinal strictures
  - Resection of ileocecal value
- Functional
  - Intestinal dysmotility syndromes
  - Hypo- or achlorhydria
  - Inflammatory conditions
  - Autonomic neuropathy
  - Reduction of gut-associated lymphoid tissue (GALT)
- Miscellaneous
  - Antisecretory and antimotility medications
  - Immunodeficiency states
  - Cirrhosis
  - Radiation enteritis
  - Diabetes mellitus
  - Chronic pancreatitis
  - Short bowel syndrome
  - End stage renal disease
  - Advanced age

Herbal Medicine

Therapeutic Goals	Herbal Medicine
Resolve bacterial overgrowth	Golden seal, barberry, phellodenrdron, thyme, myrrh, garlic, pomegranate, oregano oil, propolis
Improve digestive function and secretions	Ginger, gentian, chen pi, feverfew, andrographis, dandelion root, peppermint, coleus, fringe tree, St. Mary's thistle, globe artichoke, iberis
Regulate colonic dysmotility - for constipation	Globe artichoke, gentian, dandelion root, barberry, licorice, rhubarb, partially hydrolysed guar gum (PHGG), yellow dock
Regulate colonic dysmotility - for diarrhoea	Slippery elm, cinnamon, green tea, raspberry leaf, pomegranate
Restore a healthy microbiome	Slippery elm, marshmallow, garlic, acacia gum, pectin, cocoa, red dragon fruit, PHGG
Reduce gastrointestinal inflammation	Boswellia, turmeric, licorice, chamomile, fenugreek, marshamallow
Heal gastrointestinal mucosa	Golden seal, licorice, marshmallow, slippery elm, myrrh, calendula, propolis
Address symptoms (bloating, flatulence, abdominal pain, stool regularity)	Peppermint, chamomile, fennel, slippery elm, cinnamon, lemon balm, iberis

Myrrh

- Antimicrobial, anti-inflammatory, vulnerary, astringent.[21]
- Myrrh has been demonstrated to have antibacterial action against multiple strains of bacteria including *Escherichia coli, Staphylococcus aureus* and *Pseudomonas aeruginosa*.[22] Dominant cultures of jejunal aspirates in SIBO patients include the aforementioned strains and *Staphylococcus species*.[23]
- Inhibits inflammation induced by lipopolysaccharide.[24]

Gentian

- A bitter tonic traditionally used to stimulate saliva, gastric and bile secretions.[21]
- Gentian's ability to stimulate digestion is likely due to amarogentin, a secoiridoid glycoside that stimulates human taste receptors, promoting digestion.[25]
- Gentian has been shown to have prokinetic actions by increasing motilin in the gastric antrum, duodenum, ileum, and jejunum, and by activating muscarinic receptors.[26]
- Indicated for the treatment of constipation, flatulence, and abdominal pain. In a study of 205 participants gentian capsules we shown to provide rapid relief of constipation, flatulence and abdominal pain.[21]
- In a study of 19 patients with inflammatory gastrointestinal conditions with elevated sIgA, gentian was shown to reduce sIgA (given at 20 drops, 3 times daily),[21] indicating modification of gastrointestinal immunity.

Ginger

- Carminative, spasmolytic, anti-inflammatory, and digestive stimulant used traditionally for flatulence and dyspepsia.[21]
- Ginger has been shown to stimulate antral contractions, reduce post prandial antral area and accelerate gastric emptying.[27]
- Ginger promotes digestion by stimulating saliva production, which promotes a rise in digestive enzymes including pancreas-lipase, amylase and proteases.[28]
- The spasmogenic effect of ginger is mediated through the direct stimulation of muscarinic receptors, which mediate human circular and longitudinal colonic smooth muscle contractions, which are important in controlling gastrointestinal smooth muscle tone.[29]

Propolis

- Vulnerary, antibacterial, immune modulating, antioxidant, indicated for gastrointestinal infection.[30]
- Propolis has a diverse range of constituents, with 300 being identified. Its major constituents consist of waxes, polyphenols and terpenoids. This diversity of constituents is attributed to preventing bacterial resistance against it.[31]
- Propolis has direct antibacterial activity and stimulates immune function against infection. Its mechanisms include interference of the cellular membrane of the microorganism including membrane permeability, disruption of membrane potential and adenosine triphosphate. In addition, propolis decreases bacterial motility.[31]
- A prebiotic that improves the intestinal barrier, which has benefit for preventing bacterial translocation, toxins and pathogens.[32]

Nutritional Medicine

*Assess iron, vitamin B12 and vitamin D status of patient, supplement if required.

Therapeutic Goals	Nutritional Medicine
Resolve bacterial overgrowth	Probiotics to support gut barrier function (*see below* for strains), *Saccharomyces boulardii*, N-acetylcysteine (NAC)
Improve digestive function and secretions	Digestive enzymes
Regulate dysmotility	Dietary fibre (*see diet section*), *Saccharomyces boulardii*
Restore a healthy microbiome	Dietary fibre (*see diet section*), probiotics to restore barrier function (*see below for strains*)
Reduce gastrointestinal inflammation	Glutamine, NAC, palmitoylethanolamide (PEA), omega-3 fatty acids, bioflavonoids, vitamin D
Heal gastrointestinal mucosa	Glutamine, zinc carnosine, vitamin A, vitamin E, vitamin C, probiotics (*see below for strains*)
Address symptoms (bloating, flatulence, abdominal pain, stool regularity)	Probiotics (*see below for strains*)
Address nutrition and nutrient deficiencies	Vitamin D, vitamin B12, iron

Digestive enzymes

- Digestive enzyme insufficiency can cause and exacerbate intestinal fermentation, maldigestion and absorption.[33]
- Clinical trials have demonstrated the efficacy of microbial derived enzymes (lipase, protease and amylase) in improving the digestion and absorption of fats, proteins and carbohydrates for the beneficial treatment of malabsorption and steatorrhea,[33,34] which may be of benefit in SIBO patients.
- Bromelain is a proteolytic enzyme that may aid in the digestion of proteins. Additionally, bromelain has been shown to exert anti-inflammatory activity in the treatment of GIT infection.[35,36]

Vitamin B12

- Vitamin B12 deficiency may occur due to consumption by anerobic bacteria in the intestinal lumen before it can be absorbed.[11]
- Periodic monitoring of B12 levels in SIBO patients should be considered.

NAC

- NAC reduces the formation of bacterial biofilms and extracellular polysaccharide matrix production, in addition to inhibiting adherence and cell viability of Gram-negative and Gram-positive bacteria.[37]
- Antioxidant and free radical scavenging.[37]

Glutamine

- Reduces intestinal permeability in healthy subjects.[38]
- Alters colonic bacteria producing a favourable profile including a reduction in Firmicutes:Bacteriodetes ratio in humans.[39]
- Activates peroxisome proliferator-activated receptor gamma (PPAR-γ), an endogenous regulator of gastrointestinal inflammation.[40]
- Glutamine combined with probiotics reduces intestinal inflammation and oxidative stress; inhibiting nitric oxide (NO) and reducing inflammatory factors tumour necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and IL-8.[41]

Probiotics

- A combination of *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24, *Lactococcus lactis* W19, *Lactococcus Lactis* W58 has been found to improve intestinal barrier function *in vitro*.[42]
- *Saccharomyces boulardii* may exert antimicrobial functions due to its ability to preserve tight junctions, reduce bacterial adherence, as well as directly inhibit bacterial growth.[43] *Saccharomyces boulardii* has also been shown to increase enzyme expression on microvilli in the GIT and down-regulate intestinal inflammation via a reduction in nuclear factor kappa B (NF-kB) and IL-8.[44]

Dietary Considerations

Identifying and removing trigger foods is important to relive gastrointestinal symptoms in SIBO patients. Other dietary considerations include:

- **A low fermentable oligosaccharide, disaccharide, monosaccharide, and polyols (FODMAP)** diet can be a useful treatment intervention, as it limits carbohydrates available for fermentation and may help to control the symptoms of SIBO.[3] It should be noted, long-term restriction of carbohydrates can negatively impact the GIT mucosa and microbiome. If significant improvement is not seen in the initial weeks of the intervention, reintroduce carbohydrates into the patient's diet and investigate alternative dietary interventions for symptom management.
- **A gluten-free or low grain diet** may be of use during the antimicrobial phase as it may help to reduce the fermentation of carbohydrates, restricting the food source for bacterial overgrowth, while helping to reduce symptoms.[1] If Coeliac disease or gluten sensitives are suspected, follow a gluten-free diet and assess symptom changes.
- **The specific carbohydrate diet (SCD)** is also used in some SIBO patients and involves the avoidance of starches, oligosaccharides and disaccharides. This is thought to 'starve' the bacterial overgrowth, however, there is currently no evidence to support this intervention.[1]
- **Identify foods and beverages that trigger symptoms** in the patient and advise the patient to avoid these foods. The elimination diet may be of use to further identify foods the patient is not aware of. Once these foods have been identified and avoided for 6 to 8 weeks, begin the process of reintroduction. Advise the patient to avoid foods they consistently react to.
- **Avoid snacking** – the prokinetic action of the MMC is only activated in a fasting state. Avoid snacking to ensure adequate activity of the MMC, which may help to improve motility and reduce the patients symptoms.[1]
- **Encourage adequate hydration** to ensure the patient does not become dehydrated from diarrhoea, or to correct stool frequency in those suffering from constipation.
- **Promote a low inflammatory, whole food diet** including the consumption of fruit (if it can be tolerated, choose low sugar fruit such as blueberries, grapes, oranges, and strawberries) and 5 serves of vegetables (3 of which are green leafy vegetables) to ensure adequate phytochemical intake and prebiotic fibre to promote the growth of beneficial bacteria.
- **A diet rich in polyphenols** (green tea, grapes, cocoa, berries, flaxseed, dark chocolate, pomegranate, red dragon fruit) may help to increase beneficial bacteria counts during the antimicrobial phase.[1]
- **Encourage the consumption of omega-3 fatty acids** (small pelagic fish, avocado, nuts, seeds and their oils), as well as adequate protein, as it is required for HCl production, digestive enzymes and phase II liver detoxification.[1] Protein and fat consumption are particularly important to maintain the patient's weight if carbohydrates are being restricted.
- **Avoid alcohol, fruit juices and sugary drinks** as they encourage bacterial growth.

Lifestyle Considerations

- **Exercise** – promotes improvement in weight gain and muscle mass; improves immune function and reduces inflammation;[45] has beneficial effects on the microbiome;[46] reduces abdominal bloating;[47] promotes healthy bone density.[48]
- **Physiotherapy** may help to improve bowel motility and bowel function.
- **Encourage healthy sun exposure** for vitamin D production (e.g. mid-morning or during the afternoon) for a short period in Summer or a longer period around midday in Winter (depending on the latitude),[49] as vitamin D deficiency is associated with SIBO.
- **Avoid or weigh up the risks/benefits** of using medication that contribute to reduced gastric acid production i.e. **PPIs**.

Further Resources

- Low FODMAP Diet Monash University: https://www.monashfodmap.com/ibs-central/i-have-ibs/starting-the-low-fodmap-diet/

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