

Clinical Update for
General Practitioners and Physicians

Inflammatory Bowel Disease

Updated 2018



Disclaimer

The document is a general guide to appropriate practice, to be followed subject to the clinician's judgment and the patient's preference in each individual case in the management of Inflammatory Bowel Disease. The clinical update is designed to provide information to assist in decision-making but is not exhaustive, nor does it cover every discrete situation. It is based on the best evidence available at the time of writing.

The document is intended primarily for the use of clinicians in Australia, while complementing recent consensus statements published by the European Crohn's and Colitis Organisation (ECCO), British Society of Gastroenterology, American Gastroenterological Association and other international organisations.

Every effort has been made to check drug dosage recommendations in this clinical update but it is still possible that errors have been missed. Furthermore, dosage recommendations are continually being revised and new adverse events recognised. Trade names used in this publication are for identification purposes only. Their use does not imply endorsement of any particular brand of drug.

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Abbreviations & Acronyms

5-ASA	5-aminosalicylic acid	IBS	Irritable bowel syndrome
AXR	Abdominal radiography	INR	International normalised ratio
BCG	Bacille Calmette-Guérin	LFT	Liver function test
BMD	Bone mineral density	MBS	Medicare Benefits Schedule
CAM	Complementary and alternative medicine	MCV	Mean corpuscular volume
CDAI	Crohn's Disease Activity Index	MMR	Measles-mumps-rubella vaccine
CMV	Cytomegalovirus	MRI	Magnetic resonance imaging
CT	Computed tomography	NSAID	Nonsteroidal anti-inflammatory drug
CRP	C-reactive protein	PBS	Pharmaceutical Benefits Scheme
DXA	Dual-emission X-ray absorptiometry	PCR	Polymerase chain reaction
ESR	Erythrocyte sedimentation rate	PSC	Primary sclerosing cholangitis
EUC	Electrolytes (sodium/potassium/chloride)/ urea/creatinine	RDW	Red cell distribution width
FBC	Full blood count	TB	Tuberculosis
FMT	Faecal Microbiota Transplantation	TGA	Therapeutic Goods Administration
FOBT	Faecal occult blood testing	TNF	Tumour necrosis factor
Hob	Haemoglobin	WBC	White blood cells
HPV	Human papillomavirus	WCC	White cell count
IBD	Inflammatory bowel disease		

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1. Overview

General

Inflammatory bowel disease (IBD) describes conditions with idiopathic, chronic, relapsing and remitting inflammation of the gastrointestinal tract. Crohn's disease (CD) and ulcerative colitis (UC) are the two most common types of IBD. UC is limited to the colon (large intestine); CD can involve any part of the gastrointestinal tract from the mouth to the anus, although it most commonly affects the small intestine and/or the colon. About 5-15% of patients with IBD affecting the colon have features of both conditions.¹ Where a clear distinction cannot be made, the disorder is now referred to as IBD unclassified (IBD-U).²

IBD leads to significant morbidity and to impaired quality of life, generally without affecting mortality.³ This results in a significant burden to society: hospital costs for 2012 were estimated to be over \$100 million per annum; productivity losses, over \$380 million pa; and total indirect costs over \$2.7 billion.⁴

It is estimated that approximately 75,000 Australians are living with IBD and over 1622 new cases are diagnosed every year, 776 with CD and 846 with UC. Australia has amongst the highest reported incidence of IBD worldwide.⁵

In high-incidence areas of the world such as northern Europe, North America, Australia and New Zealand, the incidence of IBD continues to rise steadily while the incidence is rising more rapidly in low-incidence areas such as southern Europe, Asia and much of the developing world.⁶ The aetiology of IBD remains incompletely understood. Genetic, infectious and other environmental factors may play a role in the dysregulation of intestinal immunity, leading to gastrointestinal injury. Research is underway to identify causal factors in the development of IBD, including finding a specific gene or a group of genes that makes a person more susceptible to IBD. CD is more common in females and in younger children than UC and

twin studies have confirmed that a genetic influence is stronger in CD than in UC.⁷

One hypothesis to explain the difference in incidence rates between developed and developing countries is that the inappropriate immune response in IBD is related to our overly clean western lives; the hygiene hypothesis proposes that a lack of exposure to infections in early life leads to increased incidence of chronic immune diseases including IBD. Perhaps related to this exposure to infections, a New Zealand study has found that exposure to dirt by having a vegetable garden in childhood is protective against IBD.⁷

IBD can be diagnosed at any age, with a typical age of onset in the twenties: the peak prevalence in Australia is reported to be among 30 to 39-year old otherwise healthy, active people.⁴ Most people living with IBD spend many productive years coping with their life-long condition. However, even when enjoying good health, people with IBD may well be concerned about their future, given the unpredictability of its clinical course, the variation in the severity and pattern of disease and the lifelong, chronic nature of the disease. The impact of IBD is likely greater as it affects mainly young people at a time when they are establishing their careers and their relationships.

The two main disease categories in IBD, Crohn's disease (CD) and ulcerative colitis (UC), have both similar and distinct clinical and pathological features.^{2,8} The two categories have many overlapping clinical, radiological, endoscopic and histological characteristics, but equally, there are clear differences in the distribution and extent of inflammation in the gastrointestinal tract (Table 1).

Both CD and UC involve inflammation of the gastrointestinal tract. The main difference between the two diseases is the area of the gut that they affect and the thickness of the gut wall involved by the inflammation.

The Australia and New Zealand Inflammatory Bowel Disease (ANZIBD) Consortium is involved in genetic research in IBD. Interested clinicians should contact the study coordinator for a list of participating sites:

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ANZIBD Consortium: <http://www.ibd.qimr.edu.au/anzibdc.html>

Box 1

Table 1: Features for differentiating between ulcerative colitis and Crohn's disease^{2,8}

Feature	UC	CD
Site of disease	Colon only	Anywhere (mouth to anus)
Pattern of inflammation	Continuous, retrograde beginning at rectum	Discontinuous (skip lesions)
Type of inflammation	Mucosal inflammation, no granulomas	Transmural inflammation, granulomas may be present
Extracolonic disease	No	Abscesses, fistulae, (perianal disease)

In CD, the inflammation can involve any part of the gastrointestinal tract, from the mouth to the anus, although it occurs mostly in the ileum, the lower part of the small bowel (ileitis), as well as the large bowel (colitis) or both (ileo-colitis). However, in any given person, it is usually stable in location over time. In UC, the inflammation affects only the colon. In CD, the whole thickness of the gut wall can be inflamed whereas UC affects only superficial layers, being confined to the colonic mucosa.^{2,8}

1.2 Crohn's Disease

The European Crohn's and Colitis Organisation (ECCO) has attempted to standardise terms used internationally to define CD so that results of clinical trials can be applied to clinical decision making.⁹ The Crohn's Disease Activity Index (CDAI) is an estimate of the clinical severity of the disease and not of the activity of inflammation.⁸ Disease phenotype is classified according to the Montreal Classification¹⁰ (Table 2).

The following terms are recommended:

Disease activity: can be grouped into mild (CDAI 150-220), moderate (CDAI 220-450) and severe (CDAI > 450).

Remission: a CDAI of < 150 for at least 12 months.

Relapse: a flare of symptoms in a patient with established CD who is in clinical remission, either spontaneously or after medical treatment. Relapse should be confirmed by laboratory tests, imaging or endoscopy in clinical practice.

Post-operative recurrence: the term is used to define the reappearance of lesions after surgical resection.

1.3 Ulcerative Colitis

UC is characterised by diffuse mucosal inflammation limited to the colon. The European Crohn's and Colitis Organisation (ECCO),² and the American College of Gastroenterology¹¹ classify UC using the Montreal classification,¹⁰ based on Truelove and Witts' criteria¹² as it reflects clinical practice.

Disease activity: clinical disease activity is grouped into mild, moderate and severe (Table 2).

Remission: complete resolution of symptoms and endoscopic mucosal healing.

Relapse: a flare of symptoms in a patient with established UC who is in clinical remission, either spontaneously or after medical treatment. Some definitions include rectal bleeding as an essential component of relapse; others include a combination of rectal bleeding with an increase in stool frequency and abnormal mucosa at sigmoidoscopy.

Table 2: The Montreal classification in Crohn's disease and ulcerative colitis¹⁰

Crohn's disease	
Age at diagnosis	A1 Less than or equal to 16 years old A2 Between 17 – 40 years old (inclusive) A3 Over 40 years old
Location	L1 Ileal L2 Colonic L3 Ileo-colonic Modifier: L4 Isolated upper GI
Behaviour	B1 Non-stricturing, non-penetrating B2 Stricturing B3 Penetrating Modifier: P Perianal disease
Ulcerative colitis	
Extent	E1 Proctitis only E2 Left-sided (distal) colitis (to splenic flexure) E3 Extensive colitis (proximal to splenic flexure, 'pancolitis')
Severity	S0 Clinical remission S1 Mild (≤ 4 bowel actions/day, no sign of systemic toxicity) S2 Moderate S3 Severe (≥ 6 bowel actions/day with sign(s) of systemic toxicity)

1.4 Inflammatory Bowel Disease - Unclassified (IBD-U)

When a definitive distinction between UC, CD or other causes of colitis cannot be made after the history, endoscopic appearances, histopathology of multiple mucosal biopsies and appropriate radiology have been considered, the condition is referred to as inflammatory bowel disease unclassified (IBD-U).

2. Recognition, Diagnosis and Differential Diagnosis

2.1 Clinical Presentation

In IBD, symptoms range from mild to severe during relapses and decrease or may disappear during remissions. Symptoms correlate, to an extent, on the location and extent of the intestinal tract involved in the disease. However, symptoms and lesions often do not match well, and repeat investigation may be required to confirm active inflammation objectively. This is important to assess and to confirm before treatment intensification. Likewise, many patients thought to be in remission (or with symptoms below their individual threshold which can be chronically reset as 'normal') may actually be harbouring active disease with ongoing risk of progressive bowel damage, and thus warrant investigation to confirm remission.

The principal symptom of UC is diarrhoea, which is commonly bloody. Associated symptoms of urgency or tenesmus may be present as UC gets more severe. Colicky abdominal discomfort/pain is frequently due to constipation or loading, proximal to the segment of active disease, but may represent toxic megacolon during severe flares. The rectum is always involved and inflammation spreads retrograde in a continuous fashion. The clinical course is marked by exacerbation and remission. On average, about 50% of patients not on effective maintenance therapy have a relapse in any given year.¹

Symptoms of CD are more heterogeneous, due to variation in disease location/extent, but typically can include abdominal pain, diarrhoea and weight loss. Systemic symptoms of malaise, anorexia or fever are more common than in UC. CD may cause intestinal obstruction due to strictures, fistulae (often perianal) or abscesses. The presentation of CD often depends on the location affected. It can present as a colitis with bloody diarrhoea and abdominal pain. When there is only ileal involvement, it may present with right iliac fossa (RIF) pain and obstructive symptoms. In the case of diffuse small bowel involvement, CD may have a more systemic presentation with weight loss, nutritional deficiencies, malabsorption and possibly fever with few specific gut symptoms.¹

The biggest delay in making a diagnosis of IBD occurs because of not suspecting it. While IBD shares many symptoms with other more common conditions such as irritable bowel syndrome (IBS), other functional bowel disorders and infectious gastroenteritides including travellers' diarrhoea, it can be suspected after a careful history and some basic investigations.

The time course of the illness, along with the presence or absence of alarm features, are the best discriminators when delineating among these common differential diagnoses. Infectious gastroenteritis is common, and usually short-lived, with an abrupt onset, with symptoms at their worst soon after starting. Contacts with similar symptoms are often identified. IBD usually has a more gradual, insidious onset with a crescendo or fluctuating pattern. If the patient is questioned carefully, symptoms are usually found to have been present for longer than initially acknowledged. IBD, especially CD, is frequently associated with constitutional symptoms such as weight loss or anorexia and, as IBD worsens the need to pass stool at night, awakening from sleep, is a symptom that is highly suggestive.

IBS is approximately 50 times more common than IBD in Australia (10-15% of the community with IBS compared to 0.3% for IBD); it is therefore the most likely differential diagnosis that requires exclusion.¹³ IBS is typically longstanding, with fluctuating severity, but without alarm features or abnormal blood tests. As discussed, the presence of nocturnal symptoms is highly suggestive of gut inflammation. In recent years, faecal calprotectin has been found to be highly accurate in discriminating between IBD and IBS in this setting, precluding the need for more expensive and invasive tests such as colonoscopy where there are no alarm symptoms, especially in younger low-risk patients.^{14,15}

Where there is diarrhoea (without blood) as the predominant feature, with or without evidence of malabsorption (iron, vitamin D or folate deficiency), coeliac disease should always be excluded, as it is also more common than IBD (1-1.5% of the community).¹⁶

2.2 Differentiating IBD from IBS

Inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS)

Many intestinal disorders have similar symptoms, which can delay an accurate diagnosis. Irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) (both Crohn's disease and ulcerative colitis) have several symptoms in common but the differences between IBD and IBS are significant. They require different management.

Symptoms in common between IBD and IBS

- chronic abdominal pain and discomfort
- urgency and bloating
- diarrhoea
- constipation
- alternating bouts of diarrhoea and constipation
- changes in bowel habits.

The differences between IBD and IBS (i.e. features suggesting IBD)

- weight loss
- elevated C-reactive protein (CRP)
- nocturnal diarrhoea (especially if wakes patient from sleep)
- blood in stools
- fever
- obstructive symptoms
- anaemia
- iron deficiency
- low albumin.

IBS is a functional gastrointestinal disorder involving disturbance in bowel function affecting the sensorimotor function of the gut. It is a syndrome with a diagnosis made on a cluster of symptoms in the absence of structural abnormalities rather than a discrete disease. People with IBS are also more likely to have other "functional" disorders such as fibromyalgia, chronic fatigue syndrome, chronic pelvic pain, and temporomandibular joint (TMJ) disorder. IBS does not produce the inflammation found in IBD, and thus a single test like faecal calprotectin (a non-invasive marker of mucosal inflammation) is very useful, given if negative it goes against IBD with a high degree of certainty. Indeed, at a cut-off concentration of 50 mg/g, the negative predictive value of faecal calprotectin for inflammatory bowel disease has been demonstrated to be as high as 98%.¹⁵ IBS does not result in permanent damage to the intestines, intestinal bleeding or the harmful complications often associated with IBD.¹⁷

People with IBS are NOT at higher risk for colon cancer, and are not more likely to develop IBD or other gastrointestinal diseases. Conversely, IBD does place some patients at risk for colon cancer, and bleeding is a common symptom.

Box 2

Because the symptoms of CD and UC are similar, it is sometimes difficult to distinguish between them, although the precise distinction between CD and UC is often not critical, as many treatment decisions are made on disease severity and location, rather than strictly by diagnosis. However, given that biologic therapies such as infliximab, adalimumab, vedolizumab and ustekinumab are available in Australia on the Pharmaceutical Benefits Scheme (PBS) with strict criteria that do vary according to the disease subtype, the distinction between diagnoses can be useful, especially with more severe disease.

There is no single test that confirms the diagnosis of IBD. The diagnosis of IBD is made from the summation of findings of a physical examination, patient history and various tests, including blood tests, stool tests, (especially faecal calprotectin) endoscopy, biopsies and imaging studies. This combination will exclude other causes and confirm a diagnosis in most cases, and will objectively assess disease extent and severity so that the most appropriate treatment course can be recommended.

2.3 Symptoms in IBD

- Bowel symptoms: stool frequency and consistency, urgency, nocturnal diarrhoea, tenesmus, rectal bleeding, abdominal pain, vomiting, fistulas, perianal disease
- Other associated symptoms: extra-intestinal manifestations (joints, skin, mouth and eye), fever, weight loss
- Symptoms occurring in the past
- Life interference: missing work or usual social activities, mood disorders
- Time course: temporal pattern (relapsing, remitting, progressive, intermittent)
- Previous appendectomy and recent infectious gastroenteritis
- Travel history
- Contact with enteric infectious illnesses
- Vaccination history
- History of risks for tuberculosis (TB) and known TB contacts
- Medications: antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs)
- Family history (IBD, coeliac disease, colorectal cancer)
- Cigarette smoking
- Sexual history
- Food intolerances.

2.4 Physical Examination in IBD

- General wellbeing
 - weight
 - body mass index
 - pulse rate
 - blood pressure
 - temperature
 - signs of anaemia
 - fluid depletion.
- Abdominal region
 - tenderness
 - distension
 - palpable masses.
- Perianal region
 - tags
 - fissures
 - fistulas
 - abscess
 - digital rectal examination.
- Oral inspection
- Extra-intestinal manifestations: inspection of the eyes, skin and joints.

The physical examination should be complemented by investigations as described in detail on the following pages.

3. Investigations

3.1 Appropriate Tests in People with Suspected IBD

There is no one test that can reliably diagnose all cases of IBD, and many people require a number of tests (or testing on more than one occasion), which may delay diagnosis, particularly where disease is mild. In mild disease, the delay is usually not overly harmful, however abnormal pathology or radiology test results should always result in referral to a specialist gastroenterologist with a view to further confirmatory tests. Fortunately, more severe cases usually present more obviously and delays should be minimal. In suspected IBD, tests are aimed at differentiating IBD from infectious gastroenteritis, IBS and coeliac disease. Investigations also help in defining disease activity and severity. Initial investigations when patients present with suggestive symptoms should include the following:

3.1.1 Laboratory Tests

Laboratory investigations should include blood and stool examination to rule out other causes of diarrhoea and inflammation.

Blood examination

Blood tests are not specific for IBD but may be done to detect and evaluate the severity of inflammation, anaemia and vitamin or mineral deficiencies associated with IBD.

- **Full blood count (FBC):** A thorough review of FBC can reveal a lot of information. It may show anaemia (sign of chronic disease or iron deficiency); a low mean corpuscular volume (MCV) (or low MCH, both suggestive of iron deficiency); a high MCV (suggesting B12 or folate deficiency or seen in patients on immunomodulators such as thiopurines); a normal MCV with a high red cell distribution width (RDW) (suggesting a dimorphic blood film, indicating deficiency of iron and folate, or folate and vitamin B12); raised white cell count (WCC) or elevated platelet count (evidence of inflammation). In addition, a blood film may reveal rouleaux formation (similar information as ESR).

- **Biochemistry:** Low albumin (inflammation and malnutrition); elevated creatinine and/or urea (evidence of dehydration); electrolyte disturbances (low magnesium, selenium, potassium, zinc) related to poor diet and/or long-standing diarrhoea.
- **Iron studies:** Low ferritin (iron deficiency). Note, if ferritin < 100 µg/L with raised CRP level, iron deficiency (known as functional iron deficiency) is still likely. A transferrin saturation <16% is also indicative of functional iron deficiency in the setting of inflammation where ferritin might be elevated. An elevated serum ferritin can be a marker of inflammation especially liver-related inflammation.¹⁸ (See also GESA Clinical update: Iron deficiency 2015, available at [http://www.gesa.org.au/resources/clinical-guidelines-and-updates/iron-deficiency/.](http://www.gesa.org.au/resources/clinical-guidelines-and-updates/iron-deficiency/))
- **Inflammatory markers:** C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) tests may be helpful in confirming suspected inflammatory activity FBC but correlate imperfectly with intestinal inflammation and disease activity. Thus, they are helpful if elevated, but normal values do not exclude the presence of even significant inflammation.
- **Coeliac antibody testing:** (including both deamidated gliadin IgG/ tissue transglutaminase IgA) is worthwhile unless history or physical examination reveals obviously non-coeliac features such as fistulas, perianal disease and bloody stool.
- **Special antibody tests:** are not helpful in the initial assessment of a suspected case and their value in routine management is yet to be determined. They are not recommended for initial testing. Anti-saccharomyces cerevisiae antibody (ASCA) and atypical perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) serological tests can help discriminate CD from UC in some situations and are being studied for their ability to predict poor prognosis in known IBD cases.¹⁹

3.1.2 Faecal Testing to Assess for Gut inflammation:

Faecal calprotectin is the most widely used neutrophil derived protein biomarker in Australia and elsewhere. It is a highly sensitive, non-invasive marker of intestinal

inflammation,¹⁷ and has therefore been shown to be useful in the following settings:

- for differentiating between people with and without current inflammation in the lower gut needing further evaluation (mainly distinguishing between people with IBS and IBD);^{15,20} and
- for monitoring patients with IBD on therapy (to determine whether there is current disease activity, risk of relapse and/or response to current type and dose of treatment); and ²⁰⁻²³
- as a surrogate, non-invasive assessment of whether mucosal healing has been achieved or for post-operative recurrence where colonoscopy may not be practicable (eg due to access, cost, patient comorbidities, patient reluctance/ refusal).^{24,25}

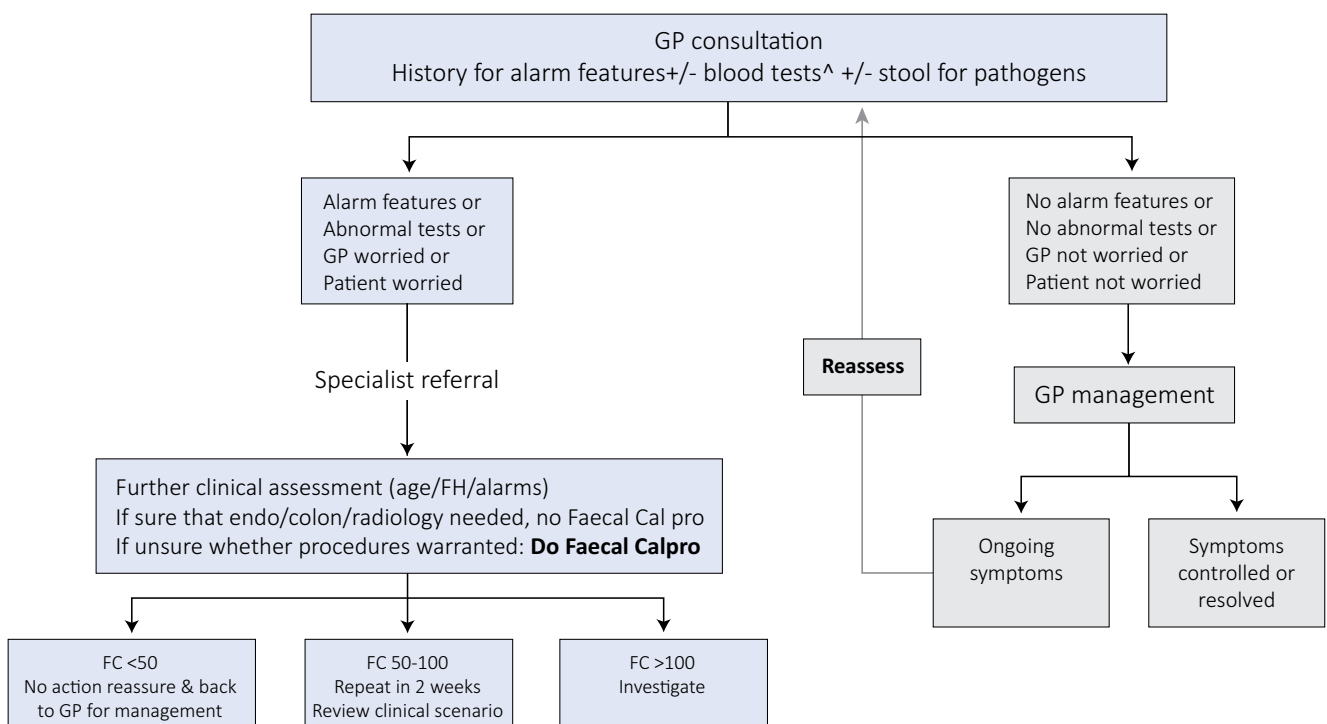
One important caveat of faecal calprotectin testing is the potential for false positives, in that the test will also be positive where there is infectious (especially bacterial) diarrhoea, and thus it is more useful to discriminate the cause of diarrhoea if restricted to clinical scenarios where diarrhoea has been present for more than 4 to 6 weeks. Although not yet MBS rebateable in Australia, faecal calprotectin is highly accurate in distinguishing IBD from

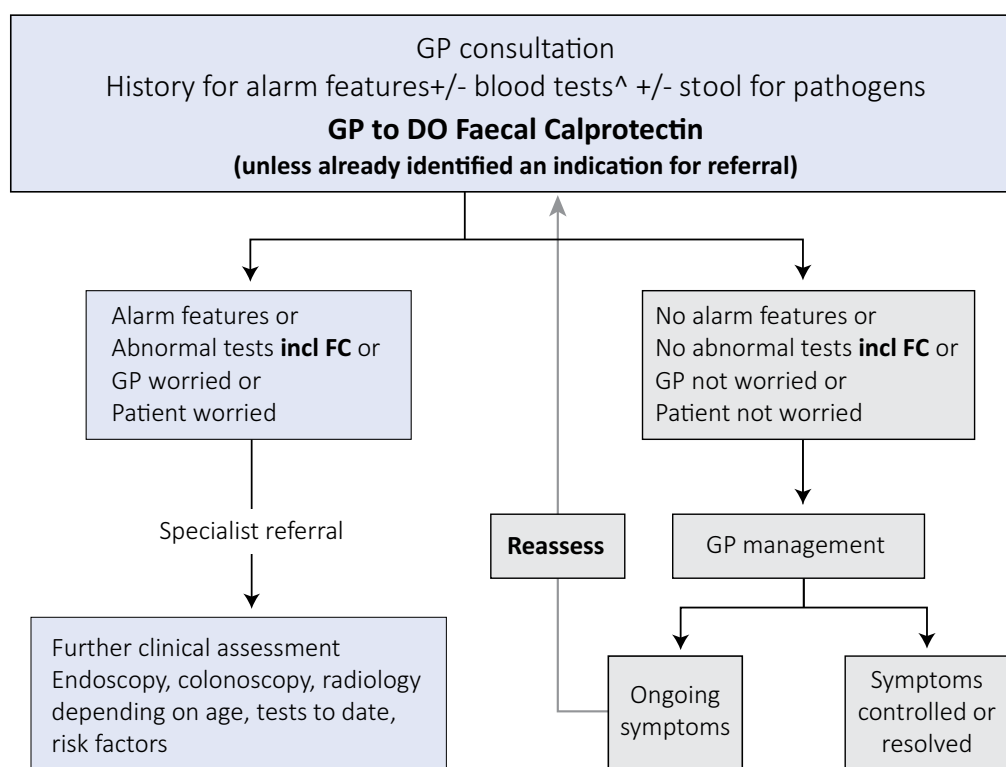
IBS,¹⁵ as depicted in the algorithm below, firstly showing the utility of calprotectin in a primary care setting or upon specialist review (Figure 1a & 1b, respectively) effectively precluding the need for further investigations such as colonoscopy or radiology if the result is negative, (where other clinical alarms are absent).

Other stool examination:

- Stool testing for pathogens in patients initially presenting with suspected IBD is also valuable as there is an increased risk of enteric infections such as *Clostridium difficile* in IBD.²⁶
- A stool examination and cultures is warranted to exclude the possibility of a bacterial, viral or parasitic cause of diarrhoea. Microbiological testing (at diagnosis, with any new flare or with bloody diarrhoea) for infectious diarrhoea should specifically include *C. difficile* toxin (especially common following antibiotic therapy, those recently hospitalized, elderly or more immunosuppressed). *C. difficile* super-infection has a higher prevalence in patients with IBD and can be more difficult to treat. Treatment of IBD with immunosuppression without addressing infectious pathogens can be dangerous, leading to a greater risk

Figure 1A & B: Algorithms demonstrating the role of faecal calprotectin in differentiating inflammatory diarrhoea (e.g. IBD) from non-inflammatory diarrhoea (e.g. IBS) and streamlining the referral and diagnostic process in patients (without alarm features) attending (A) their specialist or (B) a GP





for emergency colectomy.²⁷ Multiple stool samples may be required to confidently exclude *C. difficile* cases if pre-test probability is high.²⁸

- White blood cells on microscopy (WBC) in stool sample: indicates an inflammatory disease but this is poorly sensitive and has largely been superseded by other tests including faecal calprotectin (above).
- Faecal occult blood testing (FOBT) can reveal traces of blood that cannot be seen with the naked eye. However, FOBT is a screening test in asymptomatic patients for colorectal cancer and **should not be used** for diagnosis of IBD.
- Additional special stool cultures may be needed for patients who have travelled abroad (seek advice from infectious diseases specialists).

3.2 Further Investigations in Suspected IBD

Endoscopy / colonoscopy with histology and radiology are all used to establish the diagnosis of IBD and to assess its severity and extent. These tests should ideally be ordered in discussion with a gastroenterologist, to ensure they are necessary, performed in the appropriate manner and, in the case of imaging, to prevent young patients from unnecessary exposure to ionising radiation, by using MRI over CT where possible. It is now understood that many

patients with IBD receive high levels of radiation, due mainly to repeated computed tomography (CT) scanning.

Barium studies should no longer be ordered before referral as they are insensitive and unnecessary in most cases and give a high radiation dose.

Many procedures are ordered by non-gastroenterologists, and are frequently not needed to guide specialist management. Where detailed cross-sectional anatomy needs to be defined, magnetic resonance imaging (MRI) is preferred, but as it is only currently rebated on the Medicare Benefits Schedule (MBS) for confirmed small bowel Crohn's disease and to assess fistulising perianal disease, this is best arranged under specialist direction.

For suspected IBD, colonoscopy with ileoscopy with multiple biopsy specimens is well established as the first-line procedure to establish the diagnosis and extent of disease.^{2,8}

3.2.1 Endoscopy

- Colonoscopy (visual exam of the lining of the entire large intestine).
 - Examine for ulcers, inflammation, bleeding, stenoses
 - Multiple biopsies from the colon and terminal ileum
 - Where there is a lack of response to usual therapy, can be used to assess for cytomegalovirus (CMV)

infection (testing on biopsies – light microscopy, immunochemistry and/or polymerase chain reaction [PCR]) if the patient is receiving chronic immunosuppressant therapy (including steroids for ≥ 2 weeks duration) or *C. difficile* infection (appearances may be suggestive, such as pseudomembranes)

- Screening colonoscopy for dysplasia surveillance (see section below)

- Upper gastrointestinal endoscopy (gastroscopy or oesophageo-gastro-duodenoscopy): for upper gastrointestinal symptoms (nausea, vomiting, epigastric pain).

3.2.2 Capsule Endoscopy (Pill-Cam)

Capsule endoscopy is a useful modality to assess for the presence, extent and severity of small bowel involvement in Crohn's disease.^{29,30} However, as it does not provide cross-sectional imaging data, it is unclear what benefit it provides over MR Enterography, and there is the potential to drive surgery if capsule retention is caused by an unexpected stricture. At the time of writing, capsule endoscopy is not rebated under the current MBS framework for the indication of inflammatory bowel disease per se. Nevertheless, a rebate is available for recurrent iron deficiency anaemia or obscure-overt GI bleeding where no cause has been found following gastroscopy and colonoscopy. Strictureing Crohn's disease is a relative contraindication to capsule endoscopy due to the risk of capsule endoscopy.

3.2.3 Imaging

Avoidance of radiation exposure should be considered when selecting imaging techniques. All imaging should be discussed with a specialist to reduce number of scans and thus minimise the potential risk of radiation-induced malignancy.¹

- **Plain abdominal radiography (AXR):**

- Can establish whether colitis is present and its extent in some cases (UC).
- Excludes toxic megacolon, with acute severe colitis.
- May give an impression of a mass in the right iliac fossa, or show evidence of small bowel dilatation or obstruction (CD).

- **Barium double-contrast enema/barium small-bowel radiography:**

- Barium imaging of the gut is now rarely used in IBD and has been replaced by colonoscopy. Small bowel barium studies are too insensitive and unreliable and have been replaced by enterography (where contrast is swallowed) or enteroclysis (where the contrast is infused via a nasogastric tube) with imaging via CT or MRI.
- Barium enemas may be helpful in rare circumstances rare situations when colonoscopy is incomplete, or to delineate the length of a colonic stricture.

- **Cross-sectional imaging - CT, ultrasonography, magnetic resonance imaging (MRI; including CT enterography and MRI enterography):**

To determine the disease extent and severity and to assess for perforating complications. Ultrasound and MRI are preferred, as the patients are often young and are likely to require repeat imaging over time. As of 2015, for patients with known small bowel Crohn's disease one MR enterography examination per year is now MBS rebateable when requested by a specialist.

- **Intestinal Ultrasound:**

Intestinal ultrasound (IUS) is an emerging technique currently offered in some tertiary centres around Australia. It permits real-time assessment of disease activity, including quantifying inflammatory burden, can assist in determining the inflammatory and fibrotic components of a stricture and can help in determining if symptoms are due to active disease or due to functional issues such as faecal loading. Intestinal ultrasound can be performed on an un-prepped bowel, is non-invasive and relatively safe, and can assist in patient engagement through demonstration of disease status. IUS has been demonstrated to have similar sensitivity and specificity to other cross-sectional imaging modalities in inflammatory bowel disease.³¹

- **Dual-emission X-ray absorptiometry (DXA):** to assess bone mineral density where needed.

- **Chest radiography:**

- exclude pulmonary tuberculosis (TB)
- look for free air under the diaphragm in case of suspected perforation.

4. Management

4.1 Identifying Patients in Need of Early Help or Aggressive Therapy

It is important to identify patients at high risk of poor outcomes when assessing for known or possible IBD. Signs indicating current severe disease or a poor prognosis can be determined from a brief history and simple clinical examination. A judgment on severity and the need for urgent referral to a gastroenterologist and possible hospitalisation can frequently be made without laboratory testing. An appropriate referral for specialist or hospital care should not be delayed while waiting for test results.

The following patients are at high risk of a poor outcome and need prompt referral for specialist gastroenterology care to prevent avoidable adverse outcomes (such as bowel resection or colectomy):³²⁻³⁶

- weight loss of more than 5 kg at presentation
- poor appetite: decreased oral intake
- unable to manage usual activities
- the need for steroids at first presentation
- hospital admission at first presentation
- long term reliance on opioids for chronic pain
- those with mood disorder or antidepressants.

Early intensification of therapy may be needed in the following high-risk patients:

- young age at onset (< 40 years)
- widespread disease (e.g. ileal and perianal disease in CD or extensive colitis in UC).

As the disease is highly variable between affected individuals, it is important to follow newly diagnosed patients closely, with frequent face-to-face visits, to allow both the patient and the treating doctor to get an understanding of the disease behaviour and severity. This approach also enables doctors to promptly identify at-risk patients- those:

- in whom the disease is responding poorly to therapy
- who have progressive disease
- with intolerance or non-adherence to therapy
- needing early treatment intensification.

This approach should minimise accumulated morbidity, which often results from delayed decision-making.

There is no cure for IBD. It is a chronic disease requiring lifelong care, usually starting in early adulthood in otherwise healthy, active people.

4.2 Goals of Therapy

The goals of treatment are to:

- treat acute disease:
 - reduce or control intestinal inflammation and if possible heal the mucosa
 - minimise side-effects and long-term adverse effects
 - eliminate symptoms (abdominal pain, diarrhoea and rectal bleeding)
- improve and maintain the patient's general wellbeing (optimising the quality of life)
- correct nutritional deficiencies
- maintain steroid-free remissions (decreasing the frequency and severity of recurrences and reliance on steroids)
- prevent complications, hospitalisation and surgery.

The therapeutic approach is similar with CD and UC, even though technically UC can be cured by surgical removal of the large intestine (colectomy) however this option is reserved for patients who are refractory to all medical treatments as it often results in a different set of symptoms, due to the loss of the large intestine with either stoma or pouch formation).

Surgical management of IBD should never be considered as a failure of medical therapy, or indeed thought of as a failure by the treating gastroenterologist. There are a wide range of scenarios, especially in CD, where surgery is entirely appropriate. The LIR!C trial, a randomised placebo-controlled study of up-front surgical resection compared to intensification of medical therapy to anti-TNF therapy in patients with limited non-complicated ileal Crohn's disease failing immunomodulatory or corticosteroids demonstrated similar efficacy, cost and quality of life between the two approaches.³⁷ Similar outcomes,

supporting a role for early surgery, have been reported by others in retrospective cohort studies.^{38,39}

The medical management of IBD is determined by:

- location of inflammation within the gastrointestinal tract
- degree of involvement
- severity of symptoms
- extra-intestinal complications
- response or lack of response to previous treatment.

Historically, IBD has been treated with a limited choice of drugs or combination of drugs. Treatment decisions have been based on a standard step-up approach: at diagnosis, mild anti-inflammatory therapy is initiated; if these measures fail, patients are offered immunomodulating agents. When active disease persists, biological agents are added. If all of these measures are unsuccessful, surgery was then considered as a last resort.

However, the treatment paradigm for IBD is rapidly evolving with growing acceptance of the need to treat beyond symptoms, to aim for mucosal healing and sustained remission, and avoid repeated use of steroids. Recent consensus guidelines advocating a treat-to-target clinical management strategy have been proposed that combine patient reported outcomes of clinical remission coupled to endoscopic healing.⁴⁰ Recent research suggests that the use of immunomodulators and anti-TNF agents can be more effective if used earlier in the course of the disease (within the first 1 to 3 years).⁴¹

Due to the availability of several more effective immunomodulatory therapies, initial assessment and management are now recommended to be directed by a specialist gastroenterologist. Then, given that a chronic care model achieves better outcomes for patients, GPs are ideally placed to monitor the treatment plan once it is in place; they have a critical role in ensuring treatment adherence and are often the first point of care for the management of new symptoms and the management of lifestyle and nutritional modifications for improving the wellbeing of patients. However, all members of the care team should work together and patients should be encouraged to participate actively in therapeutic decisions.

4.3 Medical Management

4.3.1 Initial Therapy and Therapy for Disease Flares

Treatment is directed not only at relieving the symptoms of IBD but also at healing the mucosa, preventing the next flare and reducing the chances that complications may develop. Treatment to control the inflammation to give the gastrointestinal tract an opportunity to heal belongs to six main categories:

- aminosalicylates (5-ASA)
- corticosteroids
- immunomodulators (azathioprine, 6-mercaptopurine and methotrexate)
- biologic agents (infliximab, adalimumab, vedolizumab and ustekinumab)
- antibiotics (metronidazole, ciprofloxacin and others).
- exclusive enteral nutrition.

4.3.1.1 5-ASA Therapy: Mesalazine preparations

These agents are more useful in UC than CD, and are the mainstay of maintaining remission in UC.⁴² This first-line therapy is typically also used to treat mild-to-moderate symptoms of active colonic IBD. 5-aminosalicylic acid (5-ASA) is the active ingredient and it is delivered to the colon in a number of ways. It must be bound to a carrier molecule or embedded in a matrix to prevent its rapid absorption in the proximal gut. These agents are more effective for colonic (as opposed to small bowel) disease. While they do relieve acute symptoms in mild to moderate colitis, their main use is for long-term maintenance of remission. They act topically on the colonic mucosa to suppress the production of numerous pro-inflammatory mediators and control inflammation.

5-ASAs can be given orally and rectally, given, in practical terms, they are essentially a topical therapy acting at the mucosal level. 5-ASA preparations available in Australia for oral use include sulfasalazine, olsalazine, balsalazide and numerous mesalazine preparations. Those available for rectal use include mesalazine enemas (liquid or foam) and suppositories. Due to PBS regulations, patients must be treated first with sulfasalazine, unless allergic to sulfur-containing medications. If this is not tolerated or causes an allergy, which is common, patients may be offered other mesalamine-containing 5-ASA agents which do not have the sulfa- moiety (generally responsible for side effects).

Sulfasalazine can cause reversible male infertility and should not be used in men trying to conceive.⁴³

A combination of oral and topical 5-ASA compounds brings patients into remission more quickly than oral therapy alone,⁴⁴ and rectal 5-ASA therapy is equivalent, if not more effective in treating distal disease than rectal steroids.⁴⁵ 5-ASAs may need to be used in combination with oral steroids when disease is more severe.⁴⁶

4.3.1.2 Corticosteroids

For patients with acute flares who are either too sick or who do not respond to adequate doses of 5-ASA therapy or are intolerant due to side-effects, oral steroid therapy should be considered (prednisolone). Corticosteroids are used for moderate-to-severe active IBD. They usually provide significant suppression of inflammation and rapid relief of symptoms. However, significant side-effects including greater susceptibility to infection should exclude their recurrent or long-term use. They are NOT effective for maintenance therapy.

The decision to treat with steroids depends on the severity of the disease and how quickly one wants to get it under control, balanced against the risk of steroid side effects. If a very sick patient does not respond to oral steroids within a few days, hospital admission is necessary for the administration of intravenous corticosteroids and/or other treatment escalation. Oral steroids should not be continued as an outpatient if the flare is not responding promptly (one should expect obvious signs of improvement within 3-5 days). Given the availability of multiple non-steroid treatment options for IBD, there is almost never a role for long term steroids as a treatment choice.

Using steroids without also commencing immunomodulators (azathioprine, 6-mercaptopurine) and/or without early anticipation of the possible need for biologic therapy may cause these patients to undergo unnecessarily long periods of prednisolone therapy with all its associated complications and greater periods of active disease, and additionally place them at increased risk of infectious complications and resections and perhaps even an increased mortality risk.⁴⁷

The use of corticosteroids is associated with side-effects such as weight gain, osteonecrosis, susceptibility to infection (after only 25 mg per day for more than 2 weeks), acne, facial hair, hypertension, glucose intolerance or

diabetes, sleep and mood disturbance and dyspepsia. Effects associated with prolonged use (usually more than 12 weeks but sometimes less) include cataracts, osteoporosis and myopathy.⁴⁶

Topically acting, oral steroids such as enteric coated budesonide (Budenofalk® or Entocort®) are helpful for mild ileal or ileocolonic Crohn's disease and matrix-encased budesonide (Cortiment®) for mild-moderate colitis.⁴⁸ However, the use of these agents in Australia is restricted by cost as they are not subsidised by the PBS. Due to minimal release, systemically beyond the enterohepatic circulation, these budesonide formulations are associated with less reduction in bone mineral density and other systemic adverse effects than prednisolone, thus may be preferred in many patients, but again should not be used as long term maintenance therapy.

Corticosteroids including budesonide are not recommended for maintenance of remission in Crohn's disease.⁸

4.4 Maintenance Therapy

Long term maintenance therapy is standard of care for the maintenance of remission in both CD and UC; hence adherence and ongoing patient education to long-term therapy is recommended to all but the mildest cases.

4.4.1 Immunomodulators

Drugs that modulate or suppress the immune system (especially azathioprine, 6-mercaptopurine and methotrexate) are commonly used to help control inflammation, maintain long term disease remission and prevent or reduce corticosteroid dependence in IBD. However, they are not ideal agents for induction of remission due to their slow onset of action (may take a minimum of 2 to 3 months for optimal response).

- **Thiopurines:** oral 6-mercaptopurine or azathioprine (minimum 8 to 12 weeks from when reached full dose to see efficacy) **or**
- **Methotrexate:** usually commenced subcutaneously, weekly dosing (minimum 6 weeks from when reached full dose to see efficacy).

It should be noted that the efficacy data for thiopurines are generally more robust than for methotrexate in both Crohn's disease and ulcerative colitis; indeed,

data for methotrexate are particularly scarce for its use in ulcerative colitis. Hence in IBD (NB in contrast to rheumatological disorders for instance), thiopurines are generally preferable as first-line immunomodulating therapy in the vast majority of patients.^{49,50}

Immunomodulators are started when:

- disease is predicted clinically or objectively assessed (e.g. endoscopically) to be severe at onset
- steroid dependence
- a second course of steroids for a relapse is needed (within 12 months of first course)
- patient has important reason to avoid further steroids (obesity, osteoporosis, diabetes, steroid-induced mental illness).

Thiopurine S-methyltransferase (TPMT) testing before thiopurine initiation

TPMT is a key enzyme involved in thiopurine metabolism and its activity influences the rate of production of the clinically active metabolites referred to as thioguanine nucleotides (TGNs). TPMT testing can be performed in two ways; genotyping and phenotyping. Genotyping: genotypic TPMT activity is generally trimodal, such that 1 in 11 Caucasian patients are heterozygous for common TPMT mutations and 1 in 300 are homozygotes or compound heterozygotes, with the remainder having normal TPMT activity. Heterozygotes have approximately 50% TPMT activity whereas homozygotes or compound heterozygotes have little to zero activity. In both, standard doses of thiopurines will lead to excessive TGN production, which carries the risk of leucopenia and, in those with no TPMT activity, this can cause life-threatening bone marrow suppression. Phenotyping is a functional analysis and measures red cell TPMT activity in the blood and can identify those with no/little activity and intermediate activity to guide dose adjustment. Limitations of genotyping include that only common mutations are measured; hence leucopenia may still occur in those with normal TPMT due to the presence of rarer mutations. Phenotyping can be affected by anaemia or red blood cell transfusion and certain medications, including 5-ASA and thiopurines. Even with TPMT testing (by either means), patients can develop cytopenias during therapy and must be advised to contact their treating team if they have fevers or other side-effects. Thus TPMT testing does not obviate the need for monitoring during therapy as neither genotypic nor phenotypic screening is able to predict all toxicities.

4.4.2 Calcineurin Inhibitors

Cyclosporin or tacrolimus. These agents are generally reserved for rescue therapy when there is a severe episode of disease not responding to high dose intravenous steroids in hospital. There are limited data apart from case series for their use in IBD.^{51,52} Therefore, these agents should only be used under the supervision of a gastroenterologist with experience in their use, they are typically drugs used as last resort and thus prior colorectal surgical consultation is recommended, as surgery is typically the next step in management.

The aim of commencing immunomodulators is to achieve and maintain steroid-free remission and to heal the mucosa.

These drugs may cause side-effects including nausea (common), vomiting and diarrhoea (uncommon). Their use has been associated with a number of specific complications including pancreatitis (thiopurines)⁵³, hepatitis, reduced white blood cell count and an increased risk of infection. Starting at a low dose and up-titrating the dose weekly until the target dose is reached may overcome the nausea and non-specific side-effects of thiopurines. Pre-medicating those on methotrexate prior to their weekly dosing with metoclopramide or another anti-nausea agent may help to minimise intolerance. Regular blood tests (FBC and EUC/LFT weekly or fortnightly) is recommended while up-titrating the dose, and regular 3-monthly monitoring should then continue indefinitely while the patient is on therapy. Patients on methotrexate should also be prescribed folate 5mg either on the other 6 days of the week or once weekly.⁵⁴

4.4.3 Biologic Therapy

For IBD, biologic agents can only be prescribed by a specialist gastroenterologist, for patients with moderate to severe IBD, where standard medical therapy has been insufficiently effective. Anti-TNF therapy can be accessed upfront through the PBS for complicated perianal Crohn's disease.

4.4.3.1 TNF-Alpha Inhibitors (*Infliximab and Adalimumab*)

There are currently two anti-tumour necrosis factor (TNF) antibodies available on the PBS for treatment of IBD: infliximab (Remicade®-originator, Inflectra® and Renflexis® – biosimilar product) and adalimumab (Humira®).

Both infliximab and adalimumab are effective in patients with both CD and UC and are approved on the PBS for selected indications. The current criteria in each case specify that they are available to patients where standard therapies have been insufficiently effective. In CD this applies to those with a high CDAI, stoma or extensive small intestinal disease or to those with complex refractory fistulising disease. For UC, infliximab is available to patients who are hospitalised with acute severe colitis and fail to respond adequately to intravenous corticosteroids, and also to UC patients with chronically active disease according to the Mayo endoscopy and/or symptom score, in whom there is intolerance to, or inefficacy from, aminosalicylates, thiopurines and/or a course of corticosteroids. Adalimumab has recently been approved by the PBS for chronically active moderate to severe UC with the same criteria.

Infliximab is given by intravenous infusion whereas adalimumab is given by subcutaneous injection. These agents block the immune system's production of TNF, a pro-inflammatory cytokine implicated in IBD.

4.4.3.2 Anti-Integrin Therapy (Vedolizumab)

Vedolizumab (Entyvio®) was approved on the PBS for both CD and UC in 2015. Vedolizumab is a gut specific humanised monoclonal antibody that binds to and inhibits $\alpha 4\beta 7$ integrin expressed on the surface of lymphocytes, preventing their binding to mucosal addressin cell adhesion molecule-1 (MAdCAM-1) expressed on vascular endothelial cells within the gastrointestinal tract. Blocking this binding prevents lymphocyte migration into intestinal tissue.⁵⁵ Based on experience thus far, it has a favourable side effect profile likely related to its gut selective mechanism of action.⁵⁶ Achieving clinical remission with vedolizumab appears to take at least 10 to 14 weeks in CD. The apparent slower onset of action of vedolizumab, compared to anti-TNF therapies, was evident in the registration GEMINI 2 and 3 studies,^{57,58} and also in recent real world data.^{59,60} Thus expectations of the time to clinical response of patients and clinicians alike should be framed appropriately. Vedolizumab is available on the PBS for both induction and maintenance therapy for moderate to severe CD and UC. However, given its gut-specific mode of action, it may not be as effective as anti-TNF agents for certain IBD subgroups, such as those with extra intestinal manifestations (e.g. arthropathy), or those with complex

perianal fistulising disease⁵⁶ –however this is currently being evaluated.⁵⁶

4.4.3.3 Ustekinumab (Stelara)

Ustekinumab (Stelara®) is a fully human immunoglobulin G1k monoclonal antibody that targets the standard p40 subunit of the cytokines IL-12 and IL-23, which are involved in the pathogenesis of CD.⁶¹ It was approved by the PBS for moderate to severe CD in 2017 after three phase III trials (UNITI-1, UNITI-2 and UNITI-IM) were published⁶². It is administered as a single intravenous loading dose titrated to patient body weight (£ 55kg 260mg, >55 to £ 85 kg 390mg and > 85kg 520mg) and followed by 8 weekly 90mg subcutaneous doses for maintenance. In the UNITI-1 and 2 studies, clinical response (defined (defined as a decrease from baseline in the CDAI score of ≥ 100 points or a CDAI score < 150) was observed in 21.5 to 55.5% of patients. Responders from UNITI-1 and 2 entered the UNITI-IM maintenance study; 53.1% of patient were in clinical remission (CDAI score < 150) at week 44. Ustekinumab was well tolerated in the UNITI studies with no significant safety signals. Ustekinumab is indicated for the management of plaque psoriasis, and as such, is an attractive option for patients that develop psoriatic disease whilst on anti-TNF therapy.

4.4.3.4 Further Considerations Regarding Biologic Therapies

Biologic drugs have been shown to be highly effective in selected patients even as first-line therapy for the treatment of IBD.^{63,64} More data are needed on whether early aggressive therapy or a step-up approach is better in the longer term for the treatment of IBD; particularly whether early aggressive therapy has a role in altering the natural history of the disease and since there are significant cost and resource considerations with this approach.^{65,66}

It is worth noting that under the current PBS guidelines, if patients with poor prognostic features are identified early, biologic therapy can be offered in the 13th week after commencing standard therapy if it is ineffective (or sooner if patients are intolerant of thiopurines and methotrexate). A proactive approach⁴⁰ is therefore recommended when assessing new patients and planning ahead is fundamentally important.

The benefit of concomitant immunosuppression remains somewhat uncertain, given the conflicting results of the Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease (SONIC), Combination of Maintenance Methotrexate–Infliximab Trial (COMMIT) and the REACT trials.⁶⁷⁻⁶⁹ Nevertheless, because of the imperative to maintain response to biologic therapies over the long term, especially in younger patients with a lifelong disease, there is a tendency to continue combination immunomodulators with their biologic, especially in the case of anti-TNF agents, where local data suggests a loss of response rate of approximately 13% per year.⁷⁰ One widely used approach is to maintain patients on combination therapy for the first 12-18 months in order to reduce the risk of loss of response due to the development of anti-drug antibodies.⁷¹ At this point consideration can be given to changing to monotherapy in patients in remission, generally continuing with the biologic, given its relative efficacy and favourable safety profile compared to the thiopurine/methotrexate. However, such decisions are best made by specialists with a specific interest in IBD on a case-by-case basis, with adequate patient education about the long-term risks and benefits, particularly as new information continues to emerge. In such situations, frequent monitoring for sub-clinical disease recurrence is recommended, ideally using non-invasive modalities such as faecal calprotectin or intestinal ultrasound.

4.4.3.5 Risks of Biologic Therapies

Biologic therapy has the potential to be associated with various adverse effects, such as infection, malignancy and immunogenicity.⁷²⁻⁷⁴ However accumulating data relating to these agents is reassuring, and, generally, the benefits outweigh the risks in most patients with IBD. The following adverse effects have been reported with the use of biological agents for IBD:

- infusion reactions (pruritus, flushing and nausea, and with certain agents, hypersensitivity/anaphylactic reactions)
- opportunistic infections
- reactivation of viral infections
- reactivation of, or primary infection with, tuberculosis
- psoriasis and other paradoxical immune-related disorders
- worsening of congestive heart failure
- demyelinating disorders
- malignancy and lymphoma.

Notably, most serious infectious complications in Australian IBD patients on an anti-TNF agent occur early in their treatment, and the majority are associated with steroid co-therapy.⁷⁵ These data are consistent with reports from the TREAT Registry which identifies steroids and opiates as pre-eminent risk factors for adverse outcomes in IBD.⁷⁶ These data emphasise the need for a thorough initial assessment for septic foci pre biologic therapy, minimising steroid and opiate co-therapy and close supervision when using biologics (and indeed all immunosuppressant's) Local screening guidelines before commencing biologics are reviewed by Connell et al.⁷⁷

4.5 Exclusive Enteral Nutrition (EEN)

Exclusive enteral nutrition is the administration of a liquid nutrition formula to meet all nutritional requirements, replacing normal diet, either orally or via nasoenteric tube. Traditionally it has been used for induction of remission in CD over a duration of 6-8 weeks, particularly in paediatric populations. A meta-analysis suggested corticosteroids are superior to EEN for induction of remission in adult CD, in contrast to children where EEN appears equivalent or even superior to corticosteroids.⁷⁸⁻⁸⁰ The mechanism underlying EEN's effectiveness remains uncertain, however, downregulation of mucosal pro-inflammatory cytokines and altering the faecal stream with resultant effects on the host's microbiome appear likely contributors.⁸¹

Use in adult patients has been limited by poor palatability, non-adherence, cost and perhaps a greater preparedness to use steroid therapy for induction compared to children, rather than a difference in efficacy per se.⁸² The most effective approach to EEN (dose/formulation/duration) remains unclear, given significant heterogeneity in studies to date. Nevertheless, clinical remission rates of 25 to 80% within 3-4 weeks of commencement have been reported.⁸² Particular situations where EEN is attractive is where corticosteroids are contraindicated or ineffective, where nutritional support is of primary concern (eg before semi-urgent bowel surgery), as an adjunct to other induction therapies such as steroids or biologics, or where patients are self-motivated and wish to trial a dietary approach in preference to IBD pharmacotherapies.

4.6 Antibiotics

Antibiotic therapy (metronidazole, ciprofloxacin, rifaximin and others) may be useful for induction of remission in

luminal CD and perhaps in UC according to recent pooled analyses,⁸³ however the quality of the data is low and the endpoint assessed is usually clinical rather than mucosal healing.

However, antibiotics are effective for the treatment of CD complications (perianal disease, fistulas, inflammatory mass, bacterial overgrowth in setting of strictures).^{8,9} Furthermore, in UC they are useful in the treatment of pouchitis which may complicate ileo-anal pouch anastomosis following total proctocolectomy.²

Nevertheless, the use of broad-spectrum antibiotics (especially fluoroquinolones such as ciprofloxacin) are associated with an increased risk of *C. difficile* infection, which is already of higher risk in IBD, especially in those on immunosuppressive therapy.⁸⁴ Accordingly, the use of antibiotics in patients with IBD should be used with caution and only based on evidence/consensus. Furthermore, there are some data that recurrent use of antibiotics, especially in childhood, may be implicated in the development of IBD, perhaps related to perturbations of the microbiome.^{85,86}

4.7 Surgery

Surgery is indicated when medical therapy can no longer control symptoms or to deal with mechanical complications such as stricture, obstruction, perforation, abscess or refractory bleeding. In select cases it should also be considered up-front in short segment ileal disease.³⁷

While surgery may not be appropriate for everyone, especially where widespread disease cannot be completely resected without compromising gut length, it is an essential part of the overall management of IBD and should be seen as an effective, proactive adjunct of therapy, not simply as a last resort. The risk of surgery for patients diagnosed with either CD or UC continues to decrease over recent decades, but over the long term (>10 years) is still in the range of 40-50% and 15-20% respectively.^{87,88}

Often therefore, resection of part of the intestine can be of benefit or necessary in CD, but it is not a cure; the disease can, and typically will, recur after surgery.⁸⁹ Close postoperative surveillance is therefore recommended to detect recurrence early. There is debate about how aggressively one should treat postoperatively when all macroscopic disease is resected. Expert opinion and

some data recommend metronidazole for 12 weeks, thiopurine therapy for those at increased risk and ideally where available an anti-TNF agent for those at highest recurrence risk. Many also advocate a colonoscopy at 6-12 months to see if a step up in therapy is warranted in order to intervene early with medical therapy before a second resection becomes necessary.^{90,91} UC is considered cured after surgery that involves the removal of the colon; however patients frequently need ongoing care in order to manage a stoma or an ileal pouch, each with their own potential complications.²

4.8 Faecal Microbiota Transplantation (FMT):

IBD is thought to arise from a dysregulation between the immune system, host genetics and the complex ecology of the gut which is thought to harbour trillions of bacteria (known collectively as the microbiome). For instance, many genes associated with the development of IBD are known to be important in the detection, processing of and immune response to gut bacteria. Studies have demonstrated common alterations and reduced diversity in the microbiome in patients with IBD (known as dysbiosis).⁹² Thus, following on from high quality evidence supporting FMT in the management of recurrent *Clostridium difficile* colitis,⁹³ interest has turned to whether FMT may also be an effective treatment for IBD, particularly for ulcerative colitis.⁹⁴

Four recently published, randomised controlled trials (RCTs) have evaluated FMT in UC.⁹⁴ These studies showed a modest compared with placebo, but it remains uncertain whether the studies' methodology, donor characteristics and number of FMT infusions performed may have contributed to the results. Nevertheless, the effect size is comparable to that seen with biologic therapies and further data are needed. Two randomized trials of FMT have recently been conducted in Australia. Paramsothy et al randomized 85 patients with active ulcerative colitis to either FMT enemas from unrelated donors daily for five days over eight weeks or placebo. The primary endpoint, steroid-free clinical remission with endoscopic response or remission at week 8, was achieved by 27% of those receiving FMT compared to 8% of placebo (p=0.021).⁹⁵ Costello et al randomized 73 patients with mild to moderate UC to either short duration, low intensity FMT from unrelated donors (day 0 via colonoscopy and then 2 enemas at day 7) and compared this to autologous FMT. 12/38 (32%) of patients achieved the primary end-point

of steroid-free remission compared to 3/55 (9%) receiving autologous FMT ($p = 0.02$).⁹⁶ There are no published RCTs of FMT in Crohn's disease.¹⁰⁵

Currently therefore, the place of FMT as an IBD therapy remains plausible yet currently still experimental. Even if shown to be effective, the magnitude of benefit may not be justifiable given the resource intensive nature of current FMT protocols, until more streamlined donation and delivery systems are tested, proven safe and effective, and made widely available.

4.9 Therapeutic Drug Monitoring in IBD

Although the arrival of biologics has revolutionised treatment of IBD in recent years, this has resulted in increased pharmaceutical costs. In the USA, the top six biologic agents already consume 43% of the outpatient Medicare drug budget. Moreover as the goals for therapy have advanced beyond symptom control to now include mucosal healing (assessed either endoscopically or non-invasively with faecal calprotectin and/or intestinal ultrasound), there are greater expectations/opportunities to maximise outcomes, optimise each drug class and minimise treatment failures. Thus, there is a need to use drugs for a lifelong disease like IBD in a high quality, cost effective manner. Hence, therapeutic drug monitoring (TDM) is now being increasingly used to help optimise IBD care in Australia and worldwide, for anti-TNF therapies and thiopurines in particular.⁹⁷

4.9.1 Thiopurine Metabolite Testing: Up to 50% of patients do not respond to standard weight-based thiopurine dosing, and up to 20% will experience one or more adverse events on these agents.^{98,99} Both thiopurines

are inactive prodrugs that are metabolized to produce the active nucleotide metabolites 6-thioguanine nucleotides (6-TGN) and also 6-methylmercaptopurine (6-MMP) which do not confer efficacy. 6TGN levels above $235 \text{ pmol} \times 10^8$ red blood cells (RBCs) have been demonstrated to be associated with increased likelihood of clinical remission, while 6-MMP levels have been shown to have no correlation with efficacy, but, rather, can be associated with hepatotoxicity especially when levels exceed $5,700 \text{ pmol} \times 10^8$ RBCs.¹⁰⁰ Therefore when utilising TDM with thiopurines, the aim is to achieve a therapeutic 6-TGN whilst avoiding higher 6-MMP levels where possible.

A subgroup of up to 30% of patients preferentially produce 6-MMP levels upon usual dose escalation of thiopurines, resulting in a high 6MMP:6TGN ratio. This results in less chance of drug efficacy and increases the risk of hepatotoxicity and/or other side effects. This population of patients are commonly referred to as 'shunters' or 'hypermethylators' and are a common cause of treatment failures.¹⁰¹

Multiple studies have shown that the addition of allopurinol (100mg daily) in combination with a reduced dose of thiopurine (usually in the order of 25-33% of the weight-based target dose) consistently increases the 6-TGN level to within the therapeutic range, whilst significantly decreasing the 6-MMP level in shunters. Furthermore, these studies have noted few serious adverse reactions with this approach, however such dosage manoeuvres should only be undertaken by experienced specialists and blood monitoring to identify toxicity is mandatory.^{99,102-104}

Further, thiopurine metabolite testing can identify non-adherent patients and be of use to minimise toxicity and has been shown to lead to better patient outcomes.¹⁰⁵

Table 3: Practical utility of thiopurine TDM in clinical decision making and optimization of these therapies

	Metabolite Result ($\text{pmol}/8 \times 10^8 \text{ RBC}$)	Interpretation	Suggested Management
Group 1	Absent / very low 6TGN Absent / very low 6MMP	Non-adherence	Patient education
Group 2	Low 6TGN (<235) / Low 6MMP (<5,700)	Under-dosed	Increased dose
Group 3	Low 6TGN (<235) / High 6MMP (>5,700)	"Shunter"	Add 100 mg allopurinol to reduced dose thiopurine
Group 4	Therapeutic 6TGN (235-450) / Low or High 6MMP	Thiopurine Refractory	Change drug class
Group 5	High 6TGN (>450) / Low or High 6MMP	Over-dosed	Reduce dose

4.9.2 Anti-TNF Drug Level and Antibody Testing:

Unfortunately, in the 70-85% of patients who initially respond to anti-TNF therapies, secondary loss of response is estimated to occur at a rate of 13% per year in infliximab-treated patients and at a similar rate in adalimumab-treated patients.¹⁰⁶ Hence rational, cost-effective usage of TNF inhibitors using strategies (including TDM) which help to achieve long-lasting efficacy without side effects, and enable regaining of response in case of failure, are warranted for multiple reasons:¹⁰⁷

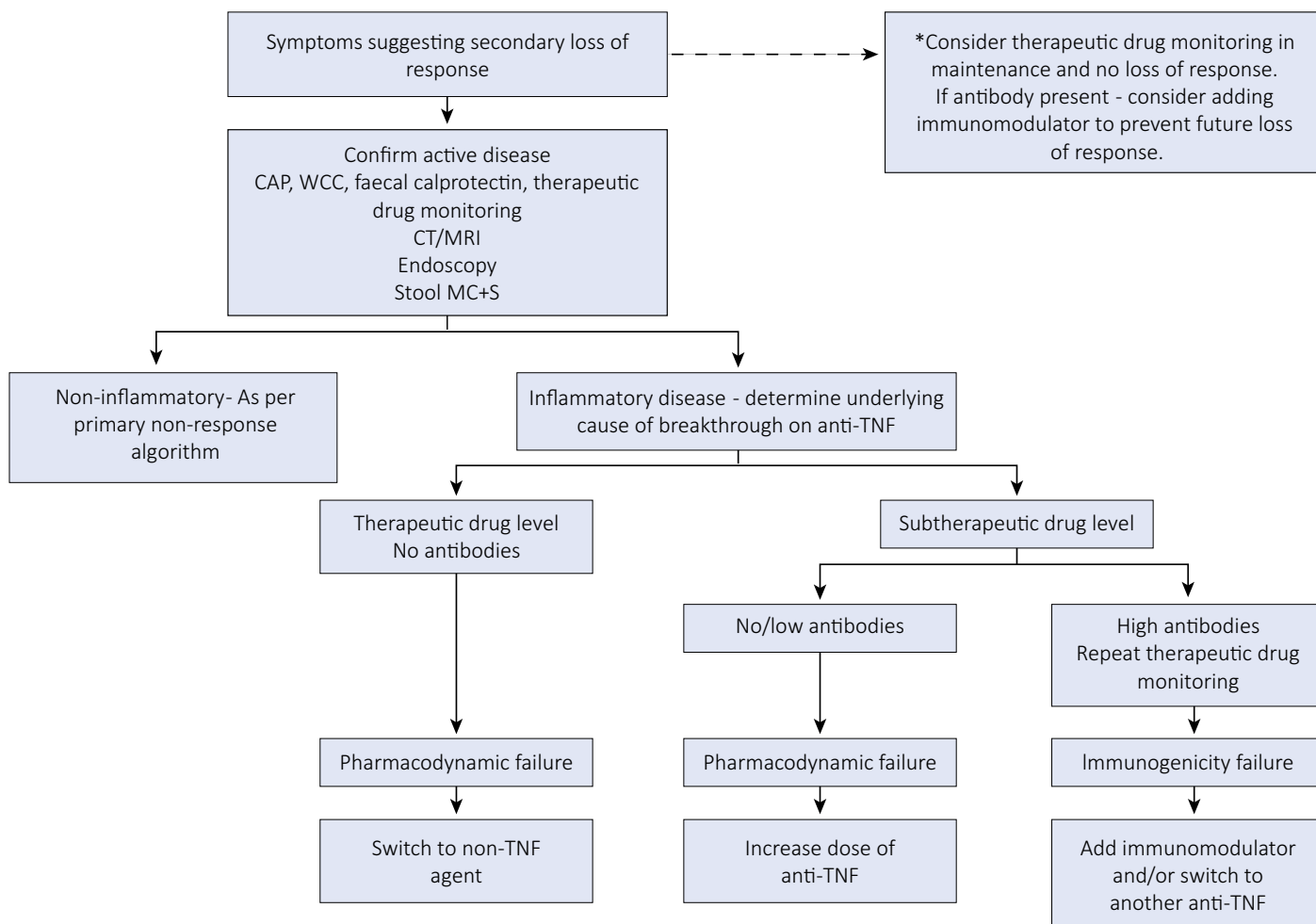
- limited alternative therapeutic options
- prolonged periods with uncontrolled disease activity can cause potentially irreversible bowel damage and disease progression
- treatment failure has immediate negative impact on patient outcomes including work productivity
- costs of continued yet ineffective anti-TNF therapies carry a heavy economic burden.

Similar to its role in thiopurines, TDM consisting of measured serum anti-TNF drug levels and anti-drug

antibodies is now widely used to inform reasons for nonresponse to anti-TNFs and better guide decision making for subsequent therapeutic choices. Australian consensus guidelines on the utility of TDM are awaited. An accepted algorithm exemplifying the utility of TDM in clinical practice is seen in Figure 2.¹⁰⁶

It should be noted that currently within Australia, there is no access to dose intensification of biologics via the PBS. Currently extra doses are either funded by health providers (eg hospitals), self-paying patients or via application for compassionate access doses from pharmaceutical companies. There is the potential for the costs of TDM-guided dose increases to be offset by dose decreases in patients where drug levels are higher than the putative therapeutic range and when therapy can be discontinued where TDM shows the patient's disease to be truly refractory in the face of very high drug levels (akin to same situation with thiopurines – see above). This has been shown in at least one study to date (TAXIT study¹⁰⁸) and is likely to become standard practice in time.

Figure 2: Proposed algorithm for use and interpretation of therapeutic drug monitoring with anti-TNF therapy.



5. Maintenance Care for People with Established IBD

5.1 Tests and Considerations in Established IBD

Tests used will depend on a patient's therapy and clinical state.

5.1.1 Well Patients Not on Immunosuppression: an annual FBE and biochemistry only is required, along with checking weight and asking about general health.

- If they have had symptomatic periods in the preceding year, consideration of treatment intensification is indicated and any symptoms or signs of possible active disease should therefore prompt testing for faecal calprotectin (see below).
- If patients have had prior low bone density or new steroid use, bone density monitoring should be considered in addition to treatment to protect bone health.
- All patients should have at least an annual review with their GP and specialist to manage their disease before problems arise and to optimise their wellbeing

5.1.2 Well Patients on Immunosuppression: need more regular consultations and should also be having routine blood tests (FBE, electrolytes (sodium/potassium/chloride)/urea/creatinine [EUC] and liver function test [LFT]). These regular visits are an opportunity to detect complications related to disease or treatment at an early stage and to identify and treat recurrent disease early. Testing patients with faecal calprotectin (see below) on a regular basis is ideal in this scenario and should be considered on a 6-12 monthly basis. The frequency of testing varies between guidelines and usual practice in different locations, but a minimal regime would be blood tests 3 monthly, visits 6 monthly with faecal calprotectin prior each (or at least every second) visit. A formal recall system is advisable: patients (and results) not seen regularly tend to be more likely to encounter problems.

5.1.3 Faecal Calprotectin in Established IBD

It is well recognised that assessment of luminal IBD disease activity, based solely on clinical grounds, is problematic. There is a poor correlation between clinical symptoms and mucosal inflammatory burden.¹⁰⁹ Functional gut disorders with symptoms that can mimic those seen in inflammatory bowel disease are common in patients with IBD. This can lead to unnecessary intensification of medical therapy which, in turn, can be associated with increased cost and the risk of adverse effects. In this context investigations are necessary to establish whether patients with IBD who have symptoms do so due to active intestinal inflammation. An ideal investigation should be one that is accessible, cost-effective, non-invasive and one with a good safety profile and acceptable to the patient. Faecal calprotectin, a non-invasive biomarker of disease activity in IBD meets these requirements and is in widespread use throughout the developed world. Further, there is a large body of data supporting the utility of faecal calprotectin in monitoring for sub-clinical disease activity and for relapse.^{22,24,25,110} Both point-of-care and ELISA based faecal calprotectin

Figure 3: Suggested algorithm for GP's monitoring patients with inflammatory bowel disease using faecal calprotectin

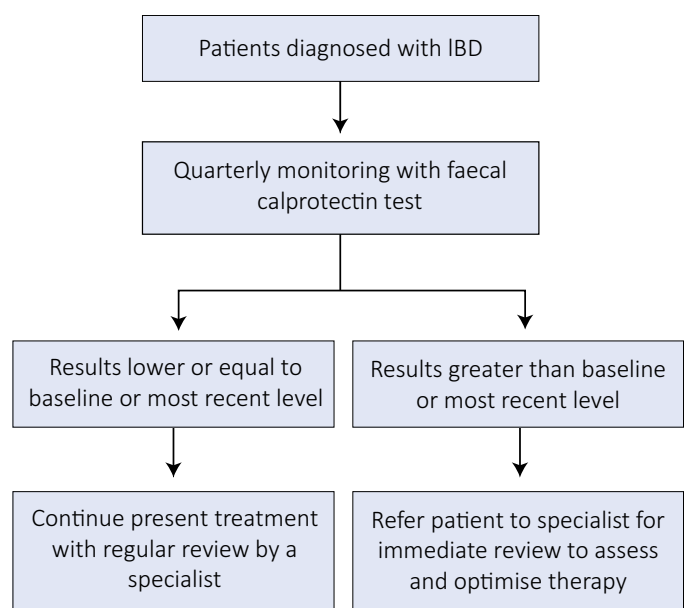
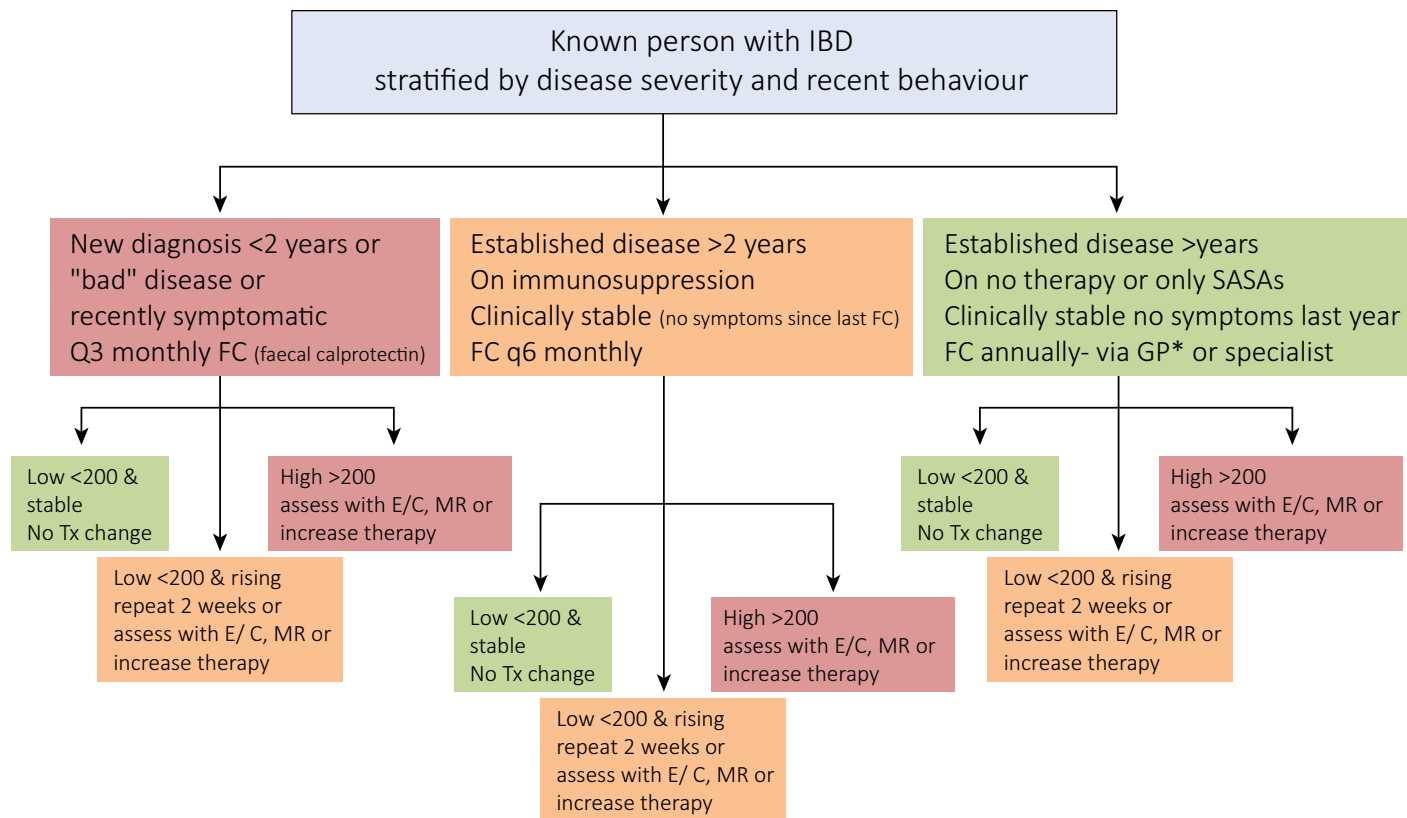


Figure 4: Proposed clinical pathway for specialist monitoring of patients with IBD



platform are recommended for monitoring of disease activity in IBD.^{2,8} Faecal calprotectin alone should not replace clinical assessment of patients with IBD, nor the use of other tests, but should be integrated into the armamentarium used by gastroenterologists who manage IBD. A suggested algorithm for GPs and specialists that incorporates the use of monitoring disease activity IBD using faecal calprotectin is shown in Figure 3 and 4

5.1.4 Patients With Longstanding (>8 years) Colitis:

As there is no clear evidence for surveillance intervals, recommendations such as that published by the NHMRC in Australia,^{111,112} are based on risk stratification:

- Annual colonoscopic surveillance is recommended for patients with ulcerative colitis extending proximal to the sigmoid colon or patients with Crohn's colitis affecting more than one third of the colon and with one or more of the following risk factors:
 - Active disease
 - Primary sclerosing cholangitis
 - Family history of colorectal cancer in first degree relative < 50 years old
 - Colonic stricture, multiple inflammatory polyps or shortened colon
 - Previous dysplasia.
- Three yearly colonoscopies recommended for patients with:
 - Inactive ulcerative colitis extending proximal to the sigmoid colon without any of the above risk factors
 - Patients with Crohn's colitis affecting more than one third of the colon without any of the above risk factors
 - IBD patients with a family history of colorectal cancer in a first degree relative > 50 years old.
- Five yearly colonoscopies recommended for patients in whom two previous colonoscopies were macroscopically and histologically normal. As suggested in the ECCO guidelines¹¹³, the surveillance schedule should take into account the risk for dysplasia to progress to CRC between two surveillance interventions. However, the timing of dysplasia progression is not known in IBD. Disease extent should be taken as the most extensive histologically-confirmed inflammation from all previous colonoscopies.¹¹³

5.1.5 Patients With Known Significant Small Intestinal

Crohn's Disease (≥ 30 cm): should have a screen for malabsorption each year including iron studies, vitamin D, B12 and folate. This screen is to avoid unsuspected complications from malnutrition, which are best prevented than treated.

5.1.6 Patients Who are Unwell: tests are aimed at defining disease activity and severity in order to guide treatment.

5.1.7 Role of the GP in Early Tests

IBD is a chronic disease and its management requires multidisciplinary care by IBD gastroenterologists, colorectal surgeons, GPs, IBD nurses, radiologists, dieticians and psychologists. Currently, most medical management is reactive and focused on acute flares of disease, although there is a push to change this approach: it is increasingly recognised that maintaining remission and anticipating problems and thereby preventing complications is a more effective strategy.

GPs have a key role in early diagnosis, supporting the patient with psychological comorbidities, assisting with smoking cessation and managing intercurrent issues such as monitoring and adherence of maintenance therapy, advice and reassurance regarding sexuality, fertility, family planning and pregnancy and early detection and management of iron deficiency and anaemia.³

GPs are encouraged to call for advice from a local gastroenterologist or IBD Service if they are uncertain about what tests are necessary before referral. If clinical suspicion and the results of the initial tests (i.e. blood tests, faecal calprotectin or imaging) suggest IBD, the patient should be referred to a hospital specialist for further tests.

Due to the delay in obtaining a routine outpatient gastroenterologist appointment in most areas of Australia, a faxed or posted referral is inadequate for any patient who is unwell. A personal phone call to the local hospital gastroenterology unit, a regional IBD Service or a local gastroenterologist is recommended as most unwell patients require review within 1-2 weeks. Most gastroenterologists will ensure priority for these patients.

Box 4

6. Routine Follow-Up

The recently published Australian IBD Standards (2016) document provides a proscriptive framework regarding the appropriate, high-quality approach to care in IBD within the Australian healthcare system.¹¹⁴

Care and follow-up of patients with IBD is a complex task requiring a multidisciplinary team and a long-term approach in treatment decisions. IBD is a life-long condition that is optimally managed as a chronic disease. Planning treatment for patients with IBD should take into account long-term outcomes as well as acute care.³ Follow-up should be individualised and should focus on those patients with signs of chronic inflammation in their mucosa.⁴⁰

6.1 GP Follow-Up

Ensure patients are in remission; if not, consider prompt referral to specialist – routine bloods and/or faecal calprotectin annually may be useful tools for annual assessment

Check adherence to medication as most non-adherence starts early after new agents are prescribed and non-adherence is the commonest cause for disease recurrence

- Identify and minimise side-effects and long-term adverse effects.
- Specifically enquire about psychosocial problems.
- Symptomatic therapy and supplements.
- Simplify drug dosing regimens (once daily is generally preferable).
- For patients on immune modifiers (azathioprine, 6-mercaptopurine): regular weekly or fortnightly blood tests (FBC and EUC/LFT) while adjusting the dose, and regular 3-monthly monitoring while the patient is on stable therapy.
- In cases of weight loss or long-term steroid use: refer for dual-energy X-ray absorptiometry (DXA) to assess bone mineral density.
- Ensure vaccinations are up to date.
- Annual influenza vaccine if on immunomodulators.
- 5 yearly pneumococcal vaccine if on immunomodulators.

- Annual PAP smear for females on any immunosuppression.
- Annual gastroenterologist review even if patients are well to ensure all eligible patients have access to new therapies and to ensure patients are truly well.
- Surveillance for colorectal cancer should be implemented in patients with long-standing extensive colonic disease: for instance cancer risk begins to be significant 8 years after the onset of extensive colitis. Colonoscopy with biopsies for dysplasia in such cases are recommended every 2-3 years.¹¹¹⁻¹¹³
- Assist with smoking cessation therapy: encourage all smokers to quit.
- Maintain good nutritional status for those with malnutrition or during periods of reduced oral intake.
- Encourage patients to actively participate in, and take responsibility for, their own management and decision-making.

6.2 Iron Deficiency, Screening for Anaemia and Treatment of Iron Deficiency

Anaemia caused by iron deficiency and also by chronic inflammation is a common systemic complication of IBD and can be one of the earliest indicators of the disease. Any patient with gastrointestinal symptoms or significant unexplained fatigue/ lethargy and iron deficiency warrants specialist referral for investigation. Iron deficiency is by far the most common nutritional problem in IBD.^{18,115,116}

Multiple factors in patients with IBD can lead to the development of anaemia, including chronic blood loss, (often occult), inadequate nutrient intake or absorption and the effect of inflammation on the bone marrow and iron handling/ transport.

Screening for anaemia

IBD patients should be regularly assessed for the presence of anaemia and deficiencies treated when necessary. Simple tests and interventions can be highly successful in improving the patient's quality of life.¹⁸ Patients with IBD should have at least an annual haemoglobin check. The ferritin, transferrin saturation and CRP should be checked in anaemic patients or those with low MCV or MCH. The

CRP is important to interpret the ferritin level as ferritin can be elevated in an acute phase reaction and transferrin saturation < 16% is also more indicative of functional iron deficiency in the setting of active inflammation. In this scenario, ferritin levels less than 100 mg/L suggest iron deficiency.¹⁸

Treatment of iron deficiency

Iron replacement should always be undertaken when deficiency found, even before establishing a specific cause.¹⁸ Treatment may be with oral iron (e.g. ferrous sulphate 200 mg up to twice a day) if tolerated or intravenous iron, with the intravenous route preferred when:

- iron deficiency is severe
- significant anaemia is present (haemoglobin <10 g/dL)
- active inflammation is present
- there is poor tolerance to oral iron
- there are problems with adherence.

Intravenous iron supplementation is available in the form of iron carboxymaltose, iron polymaltose or iron sucrose. 1 gram of iron carboxymaltose can be safely administered as a rapid IV infusion over 20 minutes and is PBS subsidised, with minimal risk of serious adverse reactions. Hence this is a very convenient and effective method of iron supplementation which can be arranged either in hospital or in the appropriately resourced GP clinic under observation.¹¹⁷

To evaluate the response to oral therapy, haemoglobin should be measured within 4 weeks in asymptomatic patients and sooner in symptomatic patients in order to ensure haemoglobin is responding appropriately and to adjust treatment. Moreover, a serum ferritin above 100 µg/L indicates appropriate iron stores in patients with IBD.¹¹⁶

IBD-associated iron deficiency and anaemia recur surprisingly fast after treatment is stopped, indicating that there may be either poor intake or ongoing active loss due to active IBD. Hence, given recurrent iron deficiency in IBD patients most likely indicates suboptimal control of their gastrointestinal inflammation, endoscopic reassessment (and/or small bowel imaging where appropriate) should therefore be considered and a careful dietary review undertaken. Iron deficiency anaemia can be due to the

development of colorectal cancer, particularly in high risk IBD patients such as those with longstanding colitis.

Other common nutritional problems can be detected by specifically looking at weight (ideally measured at every clinic visit), albumin, B12 and folate levels. Less commonly, deficiencies of other elements are sometimes seen in severely unwell patients with extensive small intestinal disease, long-standing diarrhoea or unusually restrictive dietary practices. In these settings, measurement of zinc, magnesium and selenium may be worthwhile and dietician referral should be considered. More information and dietary advice for chronic gastrointestinal disease is available on the GESA website (Resources – Patient Information).

Caution

- Oral iron therapy: non-absorbed ferrous iron has the potential to worsen IBD and other gastrointestinal symptoms, and to aggravate intestinal inflammation.¹¹⁷
- As there are now many well-tolerated forms of iron for intravenous use, intramuscular iron is not endorsed.

6.3 Psychological Issues

It is well recognised that patients with IBD are at high risk of psychological co-morbidities, especially anxiety and depression, with increased rates during disease flares.¹¹⁸ A cross-sectional Australian study in gastroenterology outpatients has shown a significant impairment of quality of life due to anxiety and depression.¹¹⁹ A history of psychological co-morbidity has been shown to be a poor prognostic factor in IBD,³³ however it is still unclear how it exerts its influence mechanistically. It is controversial whether stress and anxiety specifically worsen IBD disease course,¹²⁰ but it is also generally agreed that improving patients' psychological state will improve their quality of life, independent of IBD activity, and thus should be specifically addressed as recommended elsewhere.¹²¹ Australian data indicate that IBD patients are disadvantaged with respect to employment, education and income, often due to disease activity impairing function during their young adult years.⁴ These considerations should be carefully assessed in the management of patients with a chronic disease, particularly with respect to private or public care and treatment decisions. Patients with a chronic disease and a care plan may be referred for

MBS-supported psychological services if they meet certain criteria.

6.4 Smoking

The strongest environmental factor so far identified in IBD is cigarette smoking.¹²² There is consistent evidence that smoking increases the risk for the development of CD, and worsens its outcome; conversely, smoking is a protective factor in UC.¹²³ Smoking in CD is associated with greater disease activity, more flares, worse postoperative relapse rates, and appears to decrease the effectiveness of biologic therapies.³ However, why smoking is an important environmental factor in the pathogenesis of IBD remains uncertain.

A highly effective approach patients can take to reduce recurrence in CD is to quit smoking. Smoking cessation is associated with a 65% reduction in the risk of a relapse as compared with continued smokers, a similar magnitude to that obtained with immunosuppressive therapy.¹²⁴

IBD clinicians should actively promote smoking cessation as therapy. Highly dependent smokers with IBD should be offered support and treatment for smoking cessation similar to other smokers in the general population.¹²⁵

6.5 Vaccinations

All doctors (GPs and specialists) caring for patients with IBD should assess the patient's vaccination status at diagnosis (and first contact when patients change doctors), and ensure necessary vaccines are kept up to date (where possible) even if the patient is on treatment. As more immunosuppression therapy is being used to treat these patients, and used earlier in the disease course, it is helpful for specialists if an accurate record of a patient's vaccination history is sent with the initial referral from the GP.

In patients on immunosuppression therapy, killed or inactivated vaccines can be used with safety, and it is recommended that IBD patients receive the influenza ('flu) vaccine every year and the pneumococcal vaccine every 5 years. Live vaccines should not be given to patients on steroids, thiopurines, biological agents or other immunosuppressant's; live vaccines can be safely used in IBD patients who are only on aminosalicylates (5-ASA) medication.¹²⁶

Research has suggested that the efficacy of immunisation can be diminished in people with IBD whose immune status is compromised by immune suppression (drugs and/or chronic inflammation). Immunosuppressive treatment like corticosteroids, immunomodulators and biologics are the mainstay of therapy to suppress or modify the immune response and limit the abnormal inflammatory process.^{127,128} As the immune system is important for fighting infections, these treatments potentially increase the risk from various bacterial, viral and fungal infections, many of which are preventable by prior vaccination.¹²⁹ People with IBD may also be at risk for infections due to underlying disease, malnutrition and surgery.

Except for live vaccines, most denatured protein, carbohydrate and killed virus vaccines may be safely given to people with IBD even when immune compromised. Encouragingly, data are now emerging that even when on immunosuppression, patients are capable of mounting a satisfactory immune response to vaccines such as the influenza and HPV vaccines.^{130,131}

Infection and immunisation history should be taken when a person is diagnosed with IBD. Even if a newly diagnosed person is not currently taking immunosuppressive treatment, he or she may be on these treatments in the future. It is important to adopt a proactive strategy and consider vaccinations early on in the disease course, ideally before people with IBD start immunosuppressive therapy.

Immunisation in people with IBD follows the recommended schedules. For specific recommendations see: The Australian Immunisation Handbook 10th Edition 2017.¹³²

In addition the following five vaccines should be considered for all people with IBD:¹²⁷

- Influenza vaccine (trivalent inactivated vaccine) (annually)
- Pneumococcal vaccine (booster may be needed after 3-5 years)
- HPV vaccine (consider in adult women on immunosuppressive medication; women with IBD have a higher risk for HPV and abnormal Pap smears)
- Hepatitis B: all IBD patients should be screened for hepatitis B infection (including hepatitis B core antibody (HBcAb), hepatitis B surface antigen (HBsAg) and

hepatitis B surface antibody (HBsAb)) before initiating immunosuppressive or anti-TNF therapy

- Varicella zoster vaccine (if there is no medical history of chickenpox, shingles, or varicella zoster virus plus varicella zoster virus serology is negative).

Caution

The following live vaccines should be avoided in patients on immunosuppression or steroids or in those about to start these therapies:

- measles-mumps-rubella (MMR)
- oral polio
- yellow fever
- live typhoid
- varicella
- Bacille Calmette-Guérin (BCG).

Box 5

6.6 Bone Health, Vitamin D and Calcium

The most serious consequence of osteoporosis is fracture, resulting from low bone mineral density (BMD). Both men and women with IBD are at risk of low bone mass and osteoporosis because of poor nutrition, low BMI, chronic inflammation, corticosteroid treatment, extensive small bowel disease or resection, age, smoking and low physical activity.^{133,134}

The management of osteoporosis prevention in people with IBD involves the effective control of the underlying disease and maintaining remission of disease, along with education on the importance of lifestyle changes such as:

- avoiding excessive alcohol
- smoking cessation
- taking regular weight-bearing exercise
- ensuring good nutrition
- avoiding steroids as far as possible.

People with IBD on corticosteroid therapy or those with reduced BMD should receive calcium and vitamin D supplements. Treatment with calcium 1000 mg/day and vitamin D (800–1000 IU/day) increases bone density in patients with IBD although it is uncertain whether calcium and vitamin D prevent fracture in this group.¹³³

Australian recommended dietary intake

Calcium (dietary and supplements): 1000 mg/day for men and women over 19 years (>1300mg/day for men > 70 years, >1300mg/day for women > 51 years)

Vitamin D (sunlight exposure and supplements): 25-hydroxyvitamin D (25-OH D) levels should remain above 50 nmol/L for younger adults aged 19-50 years

Calcium and vitamin D: to optimise clinical efficacy, calcium should be taken in conjunction with vitamin D

Source: Nutrient reference values for Australia and New Zealand including recommended dietary intakes. NHMRC Canberra: Commonwealth of Australia, 2014.¹³⁵

Box 6

The diagnosis of osteoporosis is based on bone densitometry (dual energy X-ray absorptiometry (DXA) scanning). Osteoporosis is defined as a T-score of less than -2.5 (people over 50 years of age) and low bone mass is defined by a Z-score of less than 2.0 (people under 50 years of age).

Patients with a low BMD and other risk factors for osteoporosis should be referred to a specialist for anti-osteoporosis treatment. Treatment should be offered if there is a reduced BMD together with other risk factors for fracture.

6.7 Travel

Often, the ability to travel is compromised by IBD because of concerns about flare-ups while travelling, about receiving medical attention in another country, being too unwell to travel and difficulties with travel insurance.

Preventive measures are necessary to minimise the risk of infection while travelling, since people with IBD are exposed to the same infections as the general population as well as opportunistic infections related to immunosuppression. These strategies include being in remission before travel, good control of environmental exposure, chemoprophylaxis when indicated and the use of a specific vaccination program to prevent endemic infections.^{127,136}

Preventive measures before travel

- Advice regarding travel (avoid areas where tuberculosis is endemic especially if taking an anti-TNF agent)
- Monitor regular vaccination status
- Check vaccinations for specific country to prevent endemic infections
- Chemoprophylaxis (to prevent malaria)
- Antibodies against hepatitis B should be checked for travel to high prevalence areas (China, Southeast Asia, and tropical Africa) or intermediate prevalence areas (Eastern Europe, the Mediterranean, Russia, and Central and South America)
- Combined hepatitis A inactivated and hepatitis B recombinant vaccine available
- Influenza vaccination: updated for specific protection at a given time
- Strict control measures are required to prevent cholera and all diarrhoeal illnesses. Routine cholera vaccination is not recommended for Australians as the risk to travellers is very low, except it may be considered for people with IBD at increased risk of severe or complicated diarrhoeal disease (The Australian Immunisation Handbook 10th Edition 2017).¹³²

Preventive measures during travel

- Avoidance of insect bites
- Strict food and water precautions (IBD patients should pay particular attention to preventing traveller's diarrhoea; there is no evidence for chemoprophylaxis for IBD travellers to prevent diarrhoea).

Yellow fever special considerations

- **Vaccination against yellow fever is mandatory when visiting 16 countries and strongly recommended for all endemic countries.**
- **The yellow fever vaccine contains live attenuated virus and is contraindicated for IBD patients who cannot stop immunosuppressants for at least 4 months.**
- **With planning, the long-lasting immunity of yellow fever vaccine allows its administration at any time that is convenient for immunosuppressant discontinuation**

Box 7

Checks after travel

- People with IBD on immunosuppressant therapy must be carefully assessed in case of fever, diarrhoea, abdominal pain or rectal bleeding when returning from or coming from developing countries
- People on maintenance therapy with steroids, immunomodulators or biologic agents who travel to developing countries are at increased risk for opportunistic infections. Intending travellers with IBD need to think carefully about the wisdom of travel to these countries. Additionally, those on maintenance steroid therapy should be discussing with their specialist strategies to get off steroids.

7. Complementary and Alternative Medicine

There is at present no internationally agreed complementary and alternative medicine (CAM) definition and classifications of CAM therapies and modalities, which makes comparison of the findings of different studies difficult. The ECCO guidelines define complementary therapy as being used together with conventional medicine, while alternative therapy is used in place of conventional medicine.^{8,121} Refer to these guidelines above for a list of alternative therapies such as antibiotics (e.g. anti-MAP therapy), helminths, and leucocytapheresis whose role remains to be established in IBD.

Many people with IBD have used some form of CAM for a number of reasons:

- a perception that gastrointestinal disorders can be righted with diet and lifestyle changes
- some CAM have anti-inflammatory properties or alter the bacterial flora in the bowel
- these products are often seen as being natural, which does not however necessarily mean safe
- anxiety about actual or potential side-effects of standard therapy
- ineffectiveness of conventional therapies
- anxiety about continuing symptoms when taking conventional therapy.

Generally, the use of complementary medicine is considered safe. However, evidence of efficacy and safety is often unavailable. Many CAM remain unregulated as they have not yet been investigated in well-designed scientific studies. Currently, few CAMs have good evidence supporting their use in treating IBD, but, after rigorous testing, some may eventually prove beneficial. To date, E Coli Nissle (Mutaflor®) and fish oil have shown some efficacy in maintenance of remission in UC and VSL#3® for maintenance of remission in pouchitis (see below).

7.1 Herbal and Nutritional Supplements

Herbal remedies are commonly used for IBD and IBS symptoms including abdominal pain, constipation and diarrhoea. Much of the research on these remedies has

been done in China. As yet, there is only limited evidence from poor quality studies that any herbal remedies might help improve IBD symptoms.¹³⁷ Even natural herbs and supplements can have side-effects and cause dangerous interactions, for example, St John's Wort can interact with immunosuppressive agents. One exception appears to be Curcumin (Turmeric) in mild to moderate UC. Several studies of curcumin for induction and maintenance of remission amongst patients with an incomplete response to 5-ASA therapy have demonstrated improvements in clinical activity and endoscopic scores.¹³⁸

7.2 Peppermint Oil (Menthe X Piperita)

Peppermint oil is used for stomach and bowel conditions (IBD and IBS). Results from several studies suggest that enteric-coated peppermint oil capsules may improve symptoms of abdominal pain, bloating and gas and, used in small doses, it appears to be safe. Possible side-effects include allergic reactions and heartburn.^{139,140}

7.3 Prebiotics

Unlike probiotics — which are beneficial live bacteria that are consumed — prebiotics are natural compounds found in plants, such as artichokes, that help fuel beneficial intestinal bacteria. Some early animal and human data suggest that prebiotics may play a role in treating IBD.^{141,142} For instance in UC this may be mediated by enhanced butyrate production.¹⁴³

7.4 Probiotics

Probiotics are live microorganisms (in most cases, bacteria) that are similar to beneficial micro-organisms found in the human gut. They are available mainly in the form of dietary supplements and foods. The most common types of these beneficial bacteria are *Lactobacilli* and *Bifidobacteria* species. A randomised controlled trial of the probiotic drug *Escherichia coli* Nissle 1917 (Mutaflor®) has shown efficacy and safety in maintaining remission equivalent to mesalazine in patients with UC.¹⁴⁴ Studies

have also been undertaken showing high dose probiotic VSL#3[®] is effective in maintaining antibiotic-introduced remission for at least a year in patients with recurrent or refractory pouchitis.¹⁴⁵ It is thought that probiotics may have a role in treating gastrointestinal conditions, boosting immunity and preventing or slowing the development of certain types of cancer. There are no high quality studies which demonstrate that probiotics are effective in inducing remission in active CD, preventing relapse of quiescent CD or preventing post-operative CD recurrence.¹⁴⁶

7.5 Acupuncture and Moxibustion

Six studies of acupuncture and moxibustion in IBD have reported modest positive outcomes, ranging from improvements in clinical based scores to objective markers including CRP and other pro-inflammatory cytokines.¹³⁸ There are multiple limitations when interpreting the data, ranging from the validity of blinding in sham acupuncture to quality of study methodology. As such, these therapies should only be considered in those unwilling, or unable, to be treated with conventional medical therapy.

7.6 Omega-3 Free Fatty Acids

Omega-3 fatty acids are a group of polyunsaturated fatty acids that are important for a number of functions

in the body. They are found in foods such as fatty fish and vegetable oils and are also available as dietary supplements (include fish oil, flaxseed oil and walnut oil). Studies show that fish oil supplements may be effective in reducing several cardiovascular disease risk factors and may help with some aspects of rheumatoid arthritis. Evidence for the health effects of omega-3s for other conditions is limited. A Cochrane review concluded that there is no significant benefit for omega-3 free fatty acids in the treatment of CD.¹⁴⁷

Omega-3s appear to be safe for most adults at low-to-moderate doses. However, fish oil supplements may cause minor gastrointestinal upset (diarrhoea, heartburn, indigestion and abdominal bloating) and at high doses can interact with certain medications, including blood thinners and drugs used for high blood pressure.

Other CAM approaches that have not been well studied for IBD but which are commonly used include hypnotherapy, meditation, reflexology, relaxation therapies and yoga.

In order to coordinate safe and effective care for people with IBD, treating clinicians should always ask about the use of CAM and advise about any potential drug interactions. Check if a particular therapy has been studied in reputable trials by visiting the websites listed in further information on CAM.

Further information on CAM

The University of Western Sydney. The National Institute of Complementary Medicine (NICM). Available at: <http://www.nicm.edu.au/>

The Therapeutic Goods Administration (TGA) maintains the Australian Register of Therapeutic Goods (ARTG), a database that includes details of all therapeutic goods, including complementary medicines that may be legally supplied in Australia. Available at: <http://www.tga.gov.au/industry/artg-searching.htm>

US National Institutes of Health. National Centre for Complementary and Alternative Medicine. Available at: <http://nccam.nih.gov/health/digestive/>

MedicinePlus A service of the US National Library of Medicine and the National Institutes of Health. Available at: http://www.nlm.nih.gov/medlineplus/druginfo/herb_All.html#A

Box 8

8. Pregnancy

As IBD is most commonly diagnosed in the 20s to 40s, many women with IBD will be of child-bearing age and receiving treatment for IBD. Studies show a lower birth rate among both men and women with IBD which suggests avoidance of pregnancy rather than inability to conceive.^{148,149} The South Australian IBD cohort reported that people considering pregnancy were concerned about adverse fetal effects of IBD medication and surgery, adverse effects of disease activity on pregnancy outcome, adverse effects of pregnancy on disease activity, congenital abnormalities and IBD inheritance.¹⁵⁰ Importantly, most children born to parents with IBD are unaffected, even when both parents have IBD.

Inactive IBD does not appear to affect the fertility of either women or men, although active CD and previous pelvic surgery or sepsis (women) have been shown to decrease fertility. None of the usual medicines for IBD is known to decrease fertility, except sulfasalazine (men), methotrexate (women and men). These effects are reversible (after three months) once the agents are ceased.

For women with IBD, overall pregnancy outcomes are slightly worse than the general population, with slightly higher rates of spontaneous abortion, preterm birth, low birth weight, intrauterine growth retardation, small-for-gestational age, congenital anomalies and stillbirth. These risks are due to active disease and can be reduced with treatment.^{149,151}

Women with IBD considering conception should discuss their situation with their specialist well before pregnancy. They should be in remission before pregnancy. Combined care with good communication between GPs,

Extremely important

Treating doctors should discuss continuing therapy and adherence with all potentially pregnant IBD patients (i.e. all women not yet postmenopausal).

- **5-ASAs, thiopurines and anti TNF antibodies can safely be continued during pregnancy**
- **Methotrexate is potentially teratogenic and should NEVER be used in those attempting conception or pregnant.**

Box 9

gastroenterologists and obstetricians is essential. Optimal disease control is necessary before and during pregnancy for both maternal and fetal health.⁴³

Treatment

Most of the adverse outcomes in pregnancy are related to active disease rather than the medicines given to control IBD. (see Table 4)

Emerging evidence suggests women with IBD on immunosuppression have a higher risk of an abnormal Pap smear associated with human papillomavirus (HPV) infection, but this is often neglected by IBD clinicians. HPV vaccination should be offered to these women and they should have yearly Pap tests.^{152,153}

There is accumulating evidence of the protective role that breastfeeding has on the development of IBD.¹⁵⁴

Table 4: Summary of commonly used medications used in IBD and safety in pregnancy and breastfeeding

Medication	Use in Pregnancy	Use in Breastfeeding	Comments
Salazopyrin (SSZ) and 5-ASA	Safe	Safe	2gm/day folate required with SSZ
Steroids (prednisolone and budesonide)	Safe	Safe	Increased maternal risks of gestational diabetes, hypertension and preeclampsia
Thiopurines (Azathioprine and 6 mercaptopurine)	Safe	Safe	Potential concerns re neonatal anaemia not confirmed with recent studies
Allopurinol	Safety uncertain	Safe	Consider original indication and current disease activity Alternatives include split dosing to reduce shunting, or reduced dose thiopurine monotherapy if on biologics
AntiTNF therapy	Safe	Safe	No safety reason to cease early. Continued therapy recommended due to risk of relapse and small risk of failure to recapture response. No live vaccinations for baby in first 12 months
Combination therapy of thiopurine/antiTNF	Safe	Safe	x2 increase in neonatal childhood infections (eg chickenpox)
Vedolizumab	limited data but likely to be safe	limited data but likely to be safe	Use only in patients with no alternatives
Metronidazole	safe	safe	Safe in meta-analysis. Use for short course
Ciprofloxacin	safe	safe- may cause diarrhoea in infant	Safe in first trimester meta-analysis
Tacrolimus	Limited data from transplant registries. Appears safe	Avoid- baby may have therapeutic levels which may lower seizure threshold	Monitor carefully for hypertension
Cyclosporine	Limited data from transplant registries. Appears safe	Avoid- baby may have therapeutic levels which may lower seizure threshold	Monitor carefully for hypertension
Ustekinumab	limited data	limited data but likely to be safe due to molecule size	Use only in patients with no alternatives
Methotrexate	Teratogen. Do not use	Unsafe- excreted in breast milk and accumulates in neonate	Cease 6 months prior to pregnancy ideally, but minimum of one ovulatory cycle

9. Quality of Care in IBD in Australia

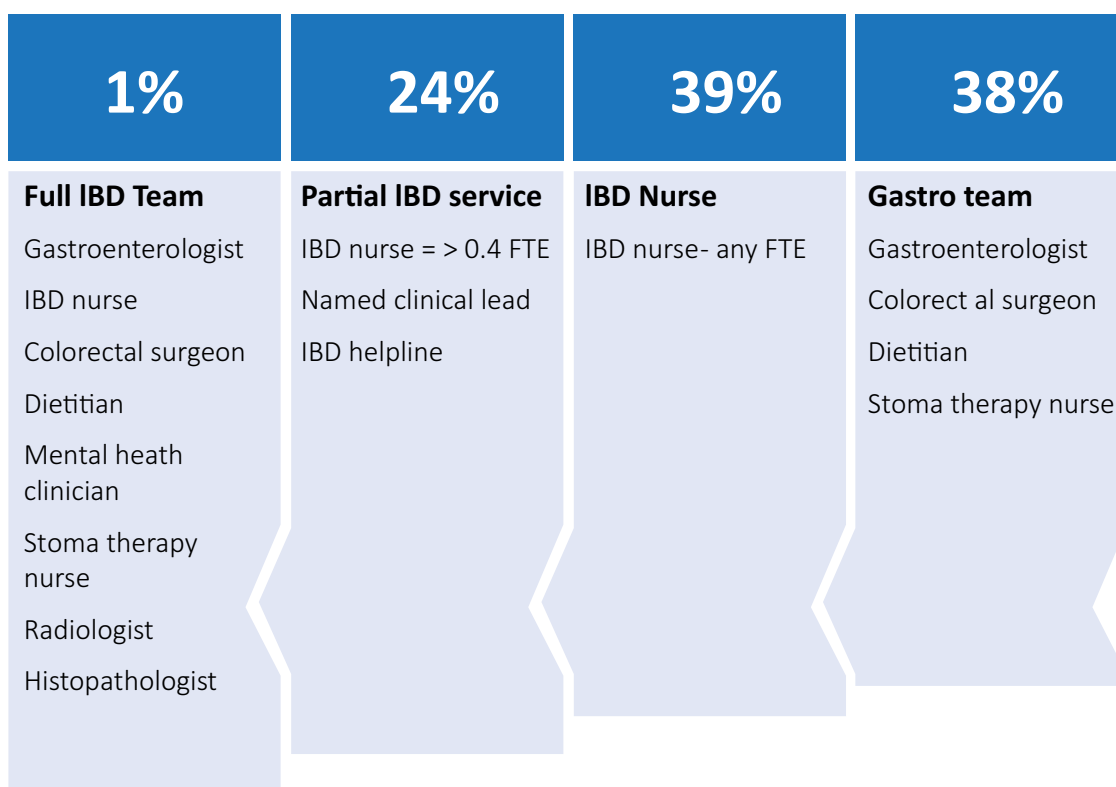
There is growing realization that achieving high standards of quality of care in IBD, akin to other chronic diseases, is integral to achieving the best possible outcomes for patients. Yet in Australia, as in many countries, there are notable variations in care received based on geography, lack of resources and lack of access to resources available. Hence, drawing on the experience and published guidelines of the UK IBD standards group and United Kingdom National Institute for Health and Clinical Excellence (NICE) who have demonstrated successful quality improvement initiatives within the UK National Health Service (NHS),^{155,156} a similar process has been commenced in Australia by the Australian IBD Quality of Care Steering Committee, representing multiple relevant stakeholders. This work has comprised the release of Australian IBD Standards 2016114, which specify consistent expectations for IBD care for hospitals, healthcare professionals and consumers. These Standards provided the benchmark for a concurrent audit of Australian IBD services which was undertaken at over 100 hospitals nationally. The audit revealed important findings,

major deficiencies and variations in quality of care, including:

- the high burden of disease, particularly in those under 40 years of age
- care is inconsistent and documentation is poor across sites, and
- full IBD teams rarely exist in Australia yet sites, even a partial IBD service is uncommon
- partial IBD services delivered better quality of care compared to hospitals without an IBD service.

Perhaps the most prominent example of the current deficiency in quality of care is that only one site throughout Australia met the full IBD standard (Figure 5) The centrality of the multidisciplinary, team-based approach to chronic disease management, yet the lack of access to this standard almost universally, as outlined by this audit process, now provides the impetus to better fund and resource the delivery of IBD services, so as to achieve better outcomes for patients.

Figure 5: Proportion of centres with documented IBD services (as defined in interim IBD standards 2015)¹⁵⁷



Importance of the IBD Specialist Nurse in Providing High Quality Care:

Recommendation 3 of the Australian IBD standards 2016 is that “IBD nurse roles should be incorporated into all IBD services in line with the proven benefit and standards.” Yet only 39% of sites participating in the Australian IBD audit had an IBD nurse on staff.

The integral role of an IBD nurse has been demonstrated in multiple studies, including in Australia by Sack et al, where after introduction of a dedicated IBD service with a specialist IBD nurse, there was a reduction in healthcare utilization and direct costs, the latter easily offsetting the cost of employing an IBD nurse several-fold.¹⁵⁸ Similarly, the introduction of a nurse to an IBD service in Cambridge, UK provided a reduction in outpatient clinic visits of approximately 40% and a reduction in total hospital length of stay by 20%.¹⁵⁹

In these and other studies, this tangible benefit provided by a nurse, regardless of the expertise of medical specialist care or other resources/ facilities available, appears to be explained by multiple aspects, including:¹⁶⁰⁻¹⁶³

- The availability of an IBD nurse-led telephone support service (as in other chronic disease states including diabetes, hypertension) allows a timely, responsive

approach to an unpredictable disease like IBD

and enables earlier intervention for problems and avoidance of emergency hospital presentations.

- The IBD nurse can provide additional education and support to patients beyond the episodic consultation with IBD specialists, thus improving adherence and outcomes.
- Safety and monitoring of medications can be more effectively achieved by the IBD nurse (e.g. thiopurine monitoring, infective screening, vaccinations).
- Given the inherent unequal relationship between the physician and patient, a nurse can often glean important information from a patient unwilling to divulge the same to their doctor and fulfil the role of confidante, thus enhancing the therapeutic relationship, quality of care, and patients' quality of life.

Therefore, in order to provide the highest quality of care to patients with IBD in Australia, and especially given access to IBD specialist doctors is often challenged by geography, limited staff and long waiting lists, and the greater complexity of management of IBD in the biologic era, it is imperative that health providers are made aware of this current major deficiency in IBD care in Australia at most centres.

Supplement 1:

IBD in the Paediatric Population

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Epidemiology of Paediatric IBD

There has been an exponential increase in the reported incidence of both CD and UC in children and adolescence, over the last 2-3 decades. This has been borne out in many regional epidemiological studies carried out in various parts of the world, including in Australia.¹⁶⁴⁻¹⁶⁶ Notably, there has been increasing reports of IBD from parts of Asia and the Middle East, traditionally thought to be low incidence regions.^{167,168} Here in Australia there are well over 5000 children with IBD.

Regarding burden of disease, in general 20-25% of patients with IBD first develop clinical disease during childhood and adolescence.¹⁶⁹ Multiple studies have shown a significant preponderance of CD in childhood when compared to UC and the reverse is true in adulthood.¹⁷⁰ There is also a predilection for males in paediatric CD but not in UC. Finally, a positive family history for IBD is more common in patients diagnosed before the age of 20.^{170,171}

Recent advancements in technology have led to better phenotyping of children and adolescents with IBD. Furthermore, it has also led to earlier diagnosis, better disease surveillance and treatment optimization. These advancements include cross-sectional imaging (e.g. MRI), endoscopy (conventional and capsule), use of inflammatory biomarkers (e.g. faecal calprotectin) and therapeutic drug monitoring (e.g. for thiopurines and biologics).

Phenotypic Differences between Paediatric/ Adolescent and Adult IBD

With regards to distribution of disease in UC, children tend to have a more extensive disease (i.e. pan-colonic) with a proportion of over 80% of cases at the time of presentation, in comparison to adults who tend to have

a left sided colitis or a Proctitis pattern in 50% of cases at diagnosis.

In children with CD, there appears to be higher reported incidence of combined ileocolonic disease than either isolated colonic or ileal disease.¹⁷²⁻¹⁷⁴ There also seems to be a higher proportion of paediatric patients diagnosed with undifferentiated (indeterminate) colitis when compared to adult populations (12% vs 6%) as shown in a large meta-analysis.¹⁷⁵ Over time, 40% of the patients with an initial diagnosis of undifferentiated colitis is reclassified to Crohn's disease.

Medical and Psychosocial Goals in Paediatric IBD

The major goals of treating children with IBD are to:

- control debilitating symptoms
- enable maximum linear growth
- maintain normal pubertal progression
- achieve maximal bone accrual and also preserve bone density
- minimize interruption of schooling and educational pursuits
- encourage continued, age-appropriate peer relationships.

With those principles in mind and to ensure the best outcomes, the therapeutic regimens utilized today usually involves early aggressive treatment and timely escalation of therapy. This in turn aims to prevent long term complications of irreversible bowel damage associated with poorly controlled disease.¹⁷⁶

Age appropriate disease activity indices such as PCDAI for Crohn's Disease and PUCAI for UC needs to be utilized by treating physicians, to aid with monitoring of disease and help streamline care. In addition, endoscopy and cross-sectional imaging should be utilized in a timely manner, performed in age-appropriate facilities and by paediatric trained personnel. Early and prompt referral to specialized multidisciplinary Paediatric IBD units is therefore strongly

encouraged, in order to achieve optimal high quality care and outcomes.¹¹⁴

Over time, the ultimate treatment goal in Paediatric IBD is also evolving towards mucosal healing. This target is shown to predict sustained clinical remission and possibly delay longer-term complications such as need for surgery and hospitalization.¹⁷⁷ Apart from the use of medication such as aminosalicylates, steroids, immunomodulators and biological agents similar to treating the adult patient with IBD (*see guidelines in Adult section*), a strong emphasis is placed on the use of exclusive enteral nutritional therapy in children when possible, particularly as an induction treatment in Crohn's Disease.⁷⁹ In general when treating children, there should be avoidance of prolonged use of corticosteroids given the direct negative impact on growth and pubertal development.¹⁷⁸

Specific nutritional needs for optimum growth will need to be assessed formally by a dietician if there are any concerns during the routine plotting of growth parameters at follow up visits (*a minimum 6 monthly documentation of height and weights in patients with IBD is recommended*). The falling of centiles may be the only indicator of poor disease control and associated malnutrition.¹⁷¹

Psychosocial Factors in Paediatric IBD

Paediatric IBD is known to affect multiple aspects of psychosocial functioning. Children and adolescents with IBD are at increased risk for internalizing disorders (e.g., depression, anxiety), poor quality of life, social and peer relationship problems, and difficulty with school-related functioning. Additionally, family dysfunction may occur

during disease flares, and both parents and siblings of a child with IBD often report distress. Many psychosocial factors are significantly related to disease activity, which suggests that assessing psychosocial problems is particularly important when the disease is active. If a child or family is experiencing significant distress in any area of psychosocial function and/or psychosocial problems are interfering significantly with life, referral to a mental health professional is strongly encouraged.¹⁷⁹

Another important difference in dealing with children with IBD is the need for awareness of the concept of family centred care and an appreciation of the burden of responsibility shouldered by parents when making long term, potentially life changing decisions for their children. All parties involved should be included in management decisions in an age-appropriate and sensitive manner.^{180,181}

Transition and Transfer of Care

Finally, a strong emphasis needs to be focussed in the domains of transition and transfer of care from the paediatric to adult services. This needs to be done in a purposeful, timely and planned manner, when the adolescent reaches an appropriate age and degree of maturity. The focus of transition is the development of self-management skills in contrast to transfer which is the change of health care providers that occurs at a distinct point in time. These processes need to be recognised as a crucial component in the care of children and adolescents which in turn will ensure the ongoing success of the care of the young adult when they finally undergo a change in their care model and treating team.¹⁸²⁻¹⁸⁴

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