Best Practice

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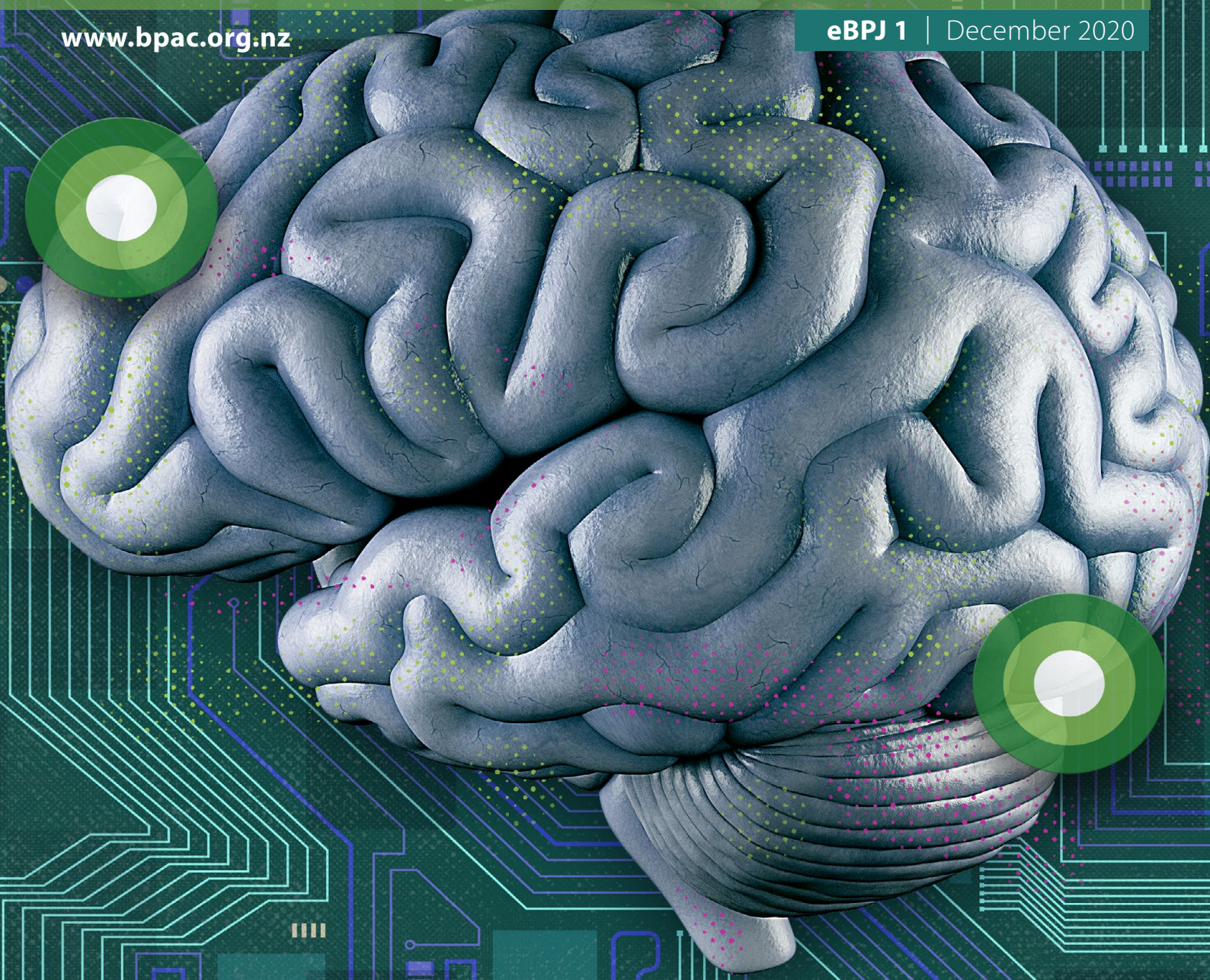
eBPJ 1 | December 2020



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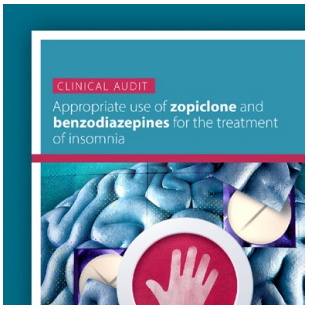
Continuing Professional Development (CPD activities)

bpac[nz] is an accredited CPD provider with the RNZCGP and InPractice. Other professional bodies also recognise our activities as continuing education. You may wish to participate in the following activities for your professional practice portfolio or for your general interest and learning.

eBPJ1 quiz

Test your general medical knowledge and recall on aspects of the articles within this journal. This is a multichoice quiz with interactive results and feedback. At the conclusion of the quiz you can print a CPD certificate as proof of participation or if you are a RNZCGP member, your continuing medical education (CME) points will be automatically allocated.

For more quizzes, visit: **https://bpac.org.nz/Mybpac/quiz**



Clinical Audit: Appropriate use of zopiclone and benzodiazepines for the treatment of insomnia

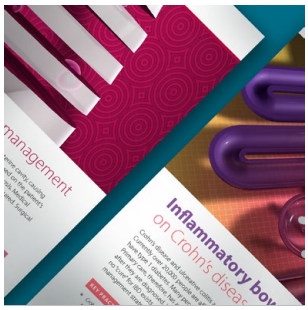
Zopiclone and some benzodiazepines, such as temazepam and triazolam, are indicated for the short-term treatment of insomnia. However, pharmacological treatment is not first-line for either of these conditions and long-term use of these medicines should be avoided where possible due to adverse effects and the potential for dependence. This audit aims to promote appropriate use of these medicines, particularly for those who are taking these medicines long-term. Advice about the risks and adverse effects and guidance on withdrawal should be given to all patients who are prescribed these medicines.

For more clinical audits, visit: **https://bpac.org.nz/audits**

Peer group discussion: Limiting the use of quinolone antibiotics

Quinolones (e.g. ciprofloxacin, norfloxacin) are associated with increasing antimicrobial resistance and rare, but potentially harmful, adverse effects. Their use should be reserved for specific indications involving serious bacterial infections, in order to protect their effectiveness. The following questions can be used as discussion points for clinical peer groups, study groups or self-reflection of practice.

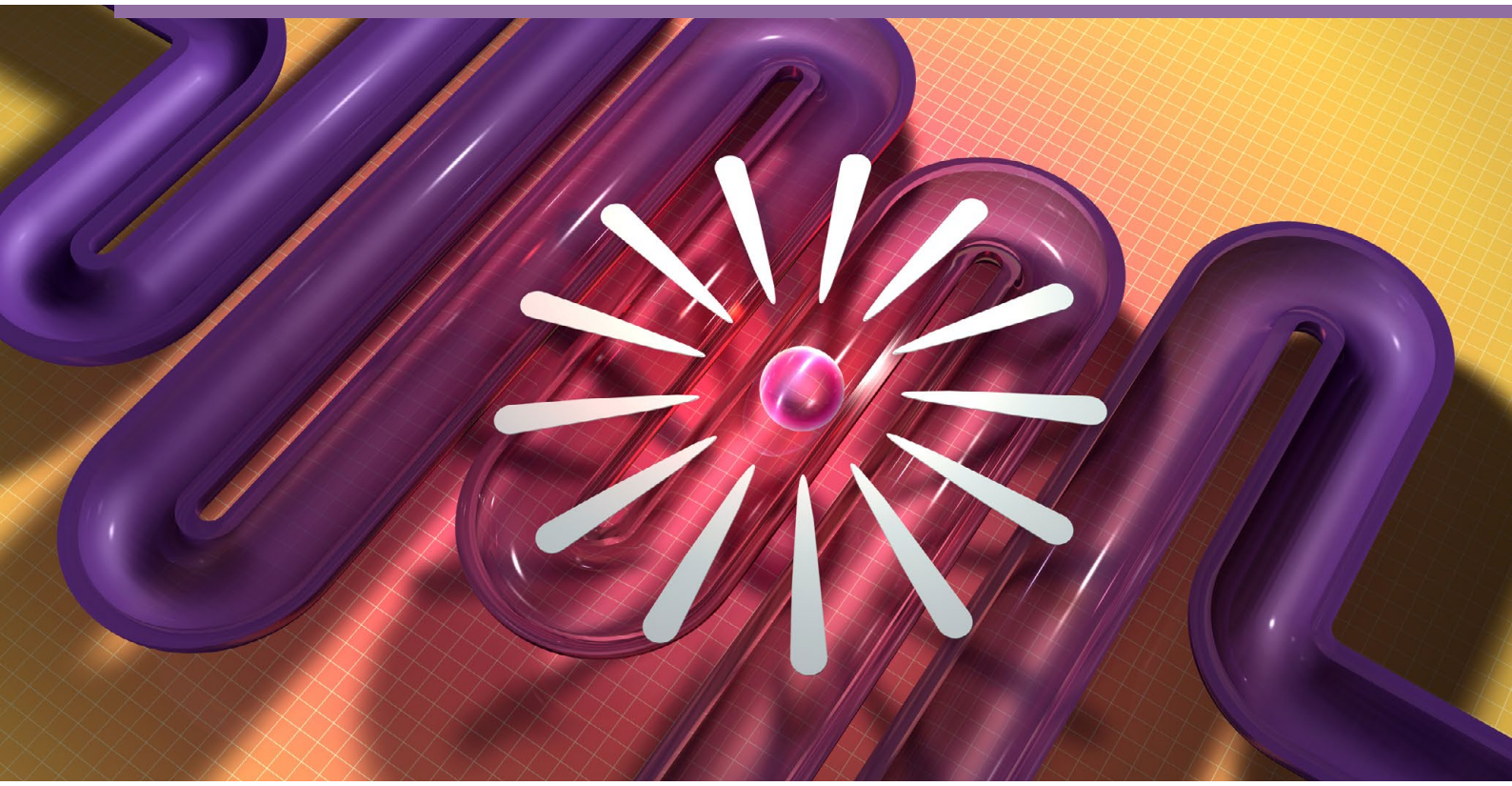
For more peer group discussions, visit: **https://bpac.org.nz/peer-group-discussions**



Reading and reflection

Reading an article in this journal or on our website is endorsed by the RNZCGP as a CPD activity. Every hour spent reading articles earns one CME credit. General Practitioners can enter a record of activity using a Learning Reflection Form, available from your dashboard on the RNZCGP website under the CME resources tab (**www.rnzcgp.org.nz**). One form is required for each article that is read.

All readers, not just general practitioners, are encouraged to reflect on what they have learnt from reading an article and may also find that it can count as a professional development activity with their own professional association, e.g. Pharmaceutical Society of New Zealand Inc, Nursing Council of New Zealand; check with your professional authorities regarding allocation of CPD credits.



Inflammatory bowel disease – a focus on Crohn's disease and ulcerative colitis

Crohn's disease and ulcerative colitis are the principal forms of chronic inflammatory bowel disease (IBD). Currently over 20,000 people are affected by IBD in New Zealand; approximately the same number as those who have type 1 diabetes. Many people with IBD are diagnosed after years of delay, resulting in worse outcomes. Primary care, therefore, has an important role in early identification of these patients, and in ongoing support after they are diagnosed, including medicines management and detection and treatment of flares. While no "cure" for IBD exists, pharmacological management of symptoms – accompanied by education and self-management strategies – can often support the patient's return to their normal daily activities.

KEY PRACTICE POINTS:

- Crohn's disease and ulcerative colitis are the two main forms of chronic inflammatory bowel disease (IBD); rates of both in New Zealand are amongst the highest in the world and are increasing due to multifactorial reasons
- The initial presentation of the two conditions can be similar, involving both bowel-specific and general symptoms; a definitive diagnosis is made using a combination of clinical, laboratory, endoscopic and histological investigations
- Medicines that can be prescribed initially in primary care for acutely unwell patients include aminosalicylates and corticosteroids, administered either orally or topically
- Patients with suspected IBD should be referred to a gastroenterologist for confirmation of the diagnosis with a colonoscopy and biopsies, and establishment of a tailored treatment regimen. Surgical procedures, or further treatment with immunomodulatory medicines, e.g. azathioprine, or biologic medicines, e.g. adalimumab, may also be required.
- Primary care clinicians have an ongoing role in the care of patients with IBD, including the management of relapse or complications, and monitoring adherence and the adverse effects of medicines
- In addition to pharmacological and surgical interventions, patients should be provided with information to optimally self-manage IBD, and equipped with strategies to cope with associated psychological and emotional effects
- A review by a dietitian is ideally required, particularly in younger patients with IBD

Crohn's disease and ulcerative colitis are chronic inflammatory bowel diseases

Inflammatory bowel disease (IBD) is an umbrella term that encompasses conditions associated with chronic inflammation of the gastrointestinal tract, of which Crohn's disease and ulcerative colitis are the principal forms, with a few cases remaining as "IBD unclassified".[1] Both conditions are characterised by a relapsing and remitting pattern of symptoms, which can vary widely between individuals, and invariably create challenges in the patient's daily routine.[1] Although there are many similarities in their presentation and management, there are significant differences in the gastrointestinal characteristics of the two conditions (see: "Making a diagnosis can be challenging").[1]

The exact cause of IBD remains uncertain

Both Crohn's disease and ulcerative colitis are believed to be triggered by environmental factors in genetically susceptible individuals – although the precise cause of either form of IBD is unknown.[2] More than 200 risk genes have been linked to IBD susceptibility, many of which are shared with other autoimmune conditions and can lead to an overly aggressive immune response.[2] Possible contributing environmental factors have been grouped under the broad concepts of "urbanisation" and a "westernised" lifestyle, including:[2, 3]

Changes to diet, i.e. the abundance and type of food (see: "IBD has become more prevalent over time" and "Diet" in the "Other aspects of management" section); obesity itself is not considered to be a risk factor for IBD development, but excess weight increases the risk of complications in people with established disease, e.g. venous thromboembolism during a flare

Access and utilisation of healthcare, e.g. antibiotic use during childhood has been associated with an increased risk of IBD, however, it is unclear if this is a causal association (specific indications and antibiotic classes have not been consistently reported between prospective investigations)

Changes to the gut microbiota (dysbiosis) – which itself may be a result of dietary change, antibiotic use or travel; for example, decreases in the prevalence of Firmicutes bacteria in the gut, as well as increases in the prevalence of Enterobacteriaceae isolates, are both associated with IBD development

Pollution/allergen exposure (including smoking) and **hygiene practices**

Hygiene practices during the early years of life are thought to be a significant contributor to the risk of developing IBD and other immune-mediated conditions (the "hygiene hypothesis").[2] Specifically, early childhood exposure to particular microorganisms, parasites and allergens is proposed to help establish immune tolerance.[2] In contrast, excessive avoidance of these factors may result in inadequate immune development.[2]

IBD has become more prevalent over time

Since the 1950s there has been a substantial increase in the number of people with IBD worldwide.[2, 4] IBD was initially thought to predominantly affect people of Western European descent, however, an increase in cases is now being observed in countries with differing ethnic distributions that previously had a low incidence of IBD, e.g. in South America, Africa and Asia. This change is likely due to urbanisation and the adoption of more western practices as described previously, e.g. diet, healthcare and hygiene, and is the driver of the net increase in incidence worldwide.[2]

New Zealand has one of the highest rates of IBD in the world; at least 20,000 people are currently estimated to be affected (one in every 227 people), approximately the same as the number of people with type 1 diabetes.[4, 5] However, given that New Zealand has no national IBD registry, timely and accurate data on prevalence is limited. In an 18-year analysis of IBD in the Otago region, 52.1% of cases diagnosed were Crohn's disease, 40.0% were ulcerative colitis and 7.9% were IBD unclassified.[6] The same study found that IBD was substantially less common in people of Māori, Pacific and Asian descent compared with Europeans, who accounted for 97.1% of all diagnoses.[6] Only 1.8% of cases were in people of Māori ethnicity, despite this group accounting for 7.5% of the Otago population.[6] Factors such as genetics, diet, healthcare access and under-diagnosis may explain differences in these ethnic trends.[5]

New Zealand is an example of a "Western" country in which the incidence of IBD continues to rise.[4] Between 2003 and 2013, the number of new IBD cases per year increased by an average of 8.1% overall.[5] Further investigation is required to understand why New Zealand differs from other Western countries where the IBD incidence rate has stabilised, despite seemingly sharing similar cultural, lifestyle, dietary and socioeconomic influences in their societies.

When to suspect IBD

Both Crohn's disease and ulcerative colitis have a peak incidence in people aged between 18 and 35 years, with a second peak of ulcerative colitis between age 60–70 years, although IBD can present in people of any age.[3, 4] Males and females are equally affected, and having a family history of

IBD should increase clinical suspicion, particularly if it involves first-degree relatives as this approximately doubles the lifetime risk.[2, 6]

The characteristic symptoms that patients with IBD present with include (also see Table 1):[1]

- **Diarrhoea** – a common feature in patients with ulcerative colitis and in most cases of Crohn's disease (N.B. people with small intestinal Crohn's disease often do not experience diarrhoea); most people with ulcerative colitis present with diarrhoea containing blood or mucus, however, the stool may be solid if there is inflammation affecting the rectum only.

  Practice point: many clinicians focus on bowel frequency, however, it is important to also ask patients with suspected IBD about the urgency of their motions and whether they have symptoms at night as these are often a more prominent concern and can have a greater impact on their quality of life, e.g. fear of not being able to reach a toilet in time or having to plan activities around toilet access.[7]

- **Other bowel symptoms** – e.g. abdominal pain, faecal incontinence, tenesmus. Less frequently there may be symptoms associated with bowel stricture or obstruction, fistulae and abscesses.
- **Non-bowel symptoms** – e.g. tiredness or malaise, fever and weight loss. Children may present with failure to thrive. Less frequently there may be skin involvement (e.g. erythema nodosum), eye involvement (e.g. episcleritis or iritis), mouth involvement (e.g. aphthous ulcers on the inside of the lips/cheeks/underneath the tongue or angular cheilitis), night sweats or primary sclerosing cholangitis

People with IBD also have an increased prevalence of other conditions associated with immune dysfunction, e.g. asthma, psoriasis, spondylarthritis and other forms of joint disease, type 1 diabetes, autoimmune hepatitis.[8] Therefore, a pre-existing diagnosis of any of these conditions may increase clinical suspicion of IBD in patients with persistent adverse bowel symptoms.

Making a diagnosis can be challenging

Research nationally and internationally shows that there is still a significant delay to diagnosis for patients with IBD.[9] In the past, diagnosis relied primarily on the histological findings from gut tissue biopsies, however, the approach has now shifted to account for multiple aspects, including the clinical presentation, laboratory investigations, endoscopic findings and histology (Table 1).[10]

If IBD is suspected after taking the history, physical examination may then reveal features that support this diagnosis, such as pallor suggestive of anaemia, mouth ulcers, abdominal tenderness, evidence of inflammation or visible anal fistula.[10] The degree of inflammation within the bowel does not always reflect symptom severity, and there is the potential to under- or over-estimate inflammation due to the subjective nature of many of the gastrointestinal symptoms. A combination of laboratory parameters, history and presentation should be used to establish disease severity, rather than relying solely on patient-reported symptoms.

It can sometimes be difficult to make a clear distinction between Crohn's disease and ulcerative colitis as there is overlap between diagnostic features (Table 1).[1] Often only colonoscopy can differentiate the two conditions. In 5–15% of patients with IBD, endoscopic and histological findings cannot distinguish between Crohn's disease and ulcerative colitis (labelled as IBD-unclassified).[1] Irrespective of the classification, IBD treatment is often the same initially, and tailored later in management.

Differential diagnoses should also be considered. Features of both main forms of IBD may overlap with other bowel conditions, including:

- Infectious diarrhoea
- Diverticulitis (more likely in patients aged >60 years)
- Colitis secondary to other causes, e.g. infection, ischaemia (in patients aged >60 years)
- Coeliac disease – usually not bloody diarrhoea
- Irritable bowel syndrome – although diarrhoea is not bloody and symptoms are usually not present at night
- Colorectal cancer

Referring patients with suspected IBD

If a diagnosis of IBD is likely then a gastroenterology assessment is required. While awaiting the appointment, medicines for symptomatic relief can be initiated immediately in primary care (see: "Medicines used in the treatment of IBD"). If needed, seek gastroenterology advice to guide medicine selection. During this time, patients should also receive education about IBD and lifestyle changes they can make (see: "Lifestyle advice for patients with IBD").

Urgent referral. In general, urgent referral to secondary care should be considered if the patient has any of the following symptoms:*

- Nocturnal symptoms, e.g. abdominal pain and diarrhoea, causing the patient to wake at night for > 2 weeks (functional diarrhoea such as irritable bowel syndrome usually stops at night)

Table 1. Distinguishing features and laboratory investigations for diagnosing IBD.[10, 11]

	Crohn's disease	Ulcerative colitis
Clinical presentation		
Diarrhoea with urgency	Frequently	Frequently
Rectal bleeding	Occasionally	Frequently
Mucus defecation	Occasionally	Frequently
Abdominal pain	Frequently	Occasionally
Abdominal mass	Sometimes in right lower quadrant	Rarely
Fever	Frequently	Uncommon (seen in severe disease)
Fatigue	Frequently (50% at the time of diagnosis; more common later in disease)	Frequently
Perianal disease	Yes	No
Endoscopic features		
Location	Can affect any part of the GI tract (but less commonly the rectum)	Always affects the rectum; extends into the colon to varying degrees
Inflammation/ ulceration	Involves deep geographic and serpiginous (snake-like) ulcers; often "patchy" transmural inflammation	Involves continuous superficial ulcers (limited to the mucosa); there is a sharp transition between diseased/ normal colon tissue
Stricture/fistulas	Yes	No
Histological features		
Fat wrapping (adipose tissue expands towards antimesenteric surface)	Frequently	Rarely
Granulomas	Occasionally	Rarely
Lymphoid aggregates	Frequently	Rarely
Crypt abscesses	Uncommon	Frequently
Patchiness	Frequently	Uncommon

Recommended laboratory investigations		
Full blood count	To detect anaemia (usually microcytic) or signs of infection (leucocytosis) or inflammation (thrombocytosis).	
C-reactive protein (CRP)	CRP will often, but not always, be raised in active IBD; CRP may correspond to severity in people with Crohn's disease but can be more variable in people with ulcerative colitis. CRP may not be raised in left-sided ulcerative colitis.	
Electrolytes	Can be important especially if diarrhoea is prominent.	
Renal function	Useful as a baseline prior to initiation of medicines.	
Liver function	Liver and bile duct abnormalities may be present in some patients with IBD. Albumin can be an important marker of malnutrition and protein-losing enteropathy.	
Stool culture	To help exclude an infectious cause of diarrhoea (including *Clostridium difficile*).	
Additional laboratory investigations to consider		
		When to consider
Faecal calprotectin	A neutrophil-derived protein regarded as the most sensitive marker of inflammation in people with IBD. Levels of faecal calprotectin often reflect disease activity but not the cause of inflammation. IBD is very unlikely if levels are <50 micrograms/g and it is considered a strong negative test for IBD. As levels of faecal calprotectin rise above 50 micrograms/g, so does the likelihood of IBD. A gastroenterologist would generally consider a level of ≥150 micrograms/g to be supportive of an IBD diagnosis; in some people, levels can be in the thousands.	■ Can be useful to support a diagnosis in some cases, however, it is costly and therefore needs to be requested appropriately ■ Strongly consider if the patient's history is consistent with IBD and a colonoscopy is not being undertaken – or the results are inconclusive – and infection/NSAID use have been excluded
Coeliac screen	Tissue transglutaminase IgA (tTG IgA) antibodies are present in nearly all people with active coeliac disease (except those with IgA deficiency).	If coeliac disease is also suspected as a differential diagnosis, e.g. symptoms align with IBD, but the patient has a family member with coeliac disease. N.B. coeliac disease does not cause bloody diarrhoea.
Thyroid stimulating hormone	Thyroid disturbances may concomitantly exist in some patients with IBD (or coeliac disease), or be an alternative explanation in patients with fatigue and bowel symptoms (thyroid dysfunction can increase intestinal motility, e.g. Graves' disease).	If features consistent with thyroid disfunction are prominent in patients with bowel symptoms, e.g. fatigue, or if coeliac disease is suspected (thyroid dysfunction occurs more frequently in patients with coeliac disease).

Urgent referral (continued)

- Severe abdominal pain or severe diarrhoea (greater than eight times a day), with or without bleeding
- Unintentional weight loss (>4.5 kg), persisting longer than four weeks
- Fever, tachycardia, hypotension, dehydration, night sweats or other symptoms of severe systemic illness alongside frequent bowel motions

These features may be indicative of complications including infection, malabsorption, strictures, obstruction, abscesses, fistulae, bleeding, perforation, and rarely toxic megacolon.

* Specific urgent referral criteria may differ across New Zealand. Refer to your local Health Pathways for region-specific guidance.

The management of IBD

Once a definitive diagnosis is reached, management can then be individualised depending on the type and severity of IBD. Traditionally, the goal of treatment has been to achieve symptomatic remission. However, the treatment target has now shifted towards the concept of "deep remission", where asymptomatic status is supported by evidence of endoscopic healing or laboratory markers.[12] Recently, faecal calprotectin has been identified as potentially a superior marker of remission in some patients compared with clinical or serum parameters, as it tends to correlate well with endoscopic and histological findings, and levels may increase in the weeks leading up to a flare.[12] However, if faecal calprotectin is not initially found to correlate with these factors, alternative markers need to be used.

IBD management includes both pharmacological and surgical interventions and colonoscopic surveillance, under the guidance of a gastroenterologist. However, given the chronic nature of IBD, primary care clinicians will continue to be involved in:

- Initial management of relapses
- Recognising and treating complications (or referring if severe)
- Reviewing and renewing prescriptions, including adherence
- Monitoring for adverse effects of treatment, e.g. three-monthly blood tests for patients on azathioprine
- Providing education and support, such as encouraging the use of Crohn's and Colitis New Zealand resources

N.B. Most DHBs have IBD nurse specialists to provide patient support, advice and follow up. Some patients may be able to communicate with their IBD healthcare team using IBDsmart, a smartphone application.

For more information on IBDsmart, see: **https://www.guthealthnetwork.com/tools-and-links/ibdsmart/**

Medicines used in the treatment of IBD

There are four main groups of medicines that are used in the treatment of IBD: aminosalicylates, corticosteroids, immunomodulatory medicines and biologics (Table 2). Selection will vary based on the type and severity of presentation, as well as patient-specific characteristics and co-morbidities. Antibiotics may also have a short-term role when inducing remission, e.g. metronidazole, but these generally are only used in patients with clear evidence of infection, e.g. abscesses in conjunction with incision and drainage or perianal fistulising disease.

Medicines for IBD are often taken orally, however, some patients with mild-to-moderate IBD limited to the rectum can also use either enema or suppository formulations of aminosalicylates such as mesalazine, or corticosteroids, e.g. hydrocortisone acetate, to deliver high concentrations directly to the inflamed mucosa.

Monitoring requirements. High medicine doses are initially used to control acute exacerbations of IBD symptoms. Once control has been achieved, the dose is reduced to balance the risk of additional flares with medicine-specific adverse effects that may occur (Table 2). As such, primary care has an important role in proactively monitoring for these adverse effects, checking the patient's adherence to their medicines and helping co-ordinate decisions around treatment escalation and de-escalation.[18]

For more information on monitoring requirements in patients with IBD treated with immunomodulatory or biologic medicines, see: **https://www.nzma.org.nz/journal-articles/new-zealand-society-of-gastroenterology-guidelines-on-therapeutic-drug-monitoring-in-inflammatory-bowel-disease**

Funded access to biologics for IBD in New Zealand remains limited. As of December, 2020, two biologics are currently funded in New Zealand for patients with severe IBD (adalimumab and infliximab).[17] Approximately two-thirds of patients who take a biologic will have a primary response to treatment, however, those who do not experience a response or have a later relapse often need to trial alternatives.[19] Internationally, ustekinumab or vedolizumab are often used as a first-line biologic for treating patients who are biologic-naïve or who have not achieved an adequate response with standard treatment. Of these two medicines, only ustekinumab is an approved medicine in New Zealand for moderate to severe Crohn's disease, but it is not funded.[1, 20]

Table 2. Fully funded medicines used in the treatment of patients with IBD.[1, 17]

<table>
<tr><th colspan="2">Group</th><th colspan="4">Medicine</th><th>Notes</th></tr>
<tr><td rowspan="5">Can be initiated in primary care</td><td rowspan="4">Aminosalicylates (ASAs)</td><td colspan="4">Mesalazine</td><td rowspan="4">• Often used first-line for the treatment of mild-to-moderate IBD (predominantly for ulcerative colitis as ASAs are much less effective in Crohn's disease)
• Oral use is the most common; topical formulations of mesalazine (either enema [for left-sided disease] or suppositories [for rectal disease]) are also available for patients with mild-to-moderate disease – this can be provided in combination with oral use
• Gastroenterologists may advise initiating an ASA (or a corticosteroid) while awaiting an assessment if IBD is likely and the patient has severe symptoms
• ASAs increase the risk of blood dyscrasias
• Patients should be advised to report any unexplained bleeding, bruising, fever, malaise, purpura, or sore throat, in addition to monitoring for medicine-specific adverse effects</td></tr>
<tr><td>Brand</td><td>Oral</td><td>Suppository</td><td>Enema</td></tr>
<tr><td>Asacol</td><td>Acute flare: 0.8–1.6 g three times daily
Maintenance: 400–800 mg three times daily</td><td>0.5–1 g up to 3 times daily, reduce dose according to response; max 1 g twice daily if using in addition to oral therapy</td><td>Not available</td></tr>
<tr><td>Pentasa</td><td>Acute flare: up to 4 g once daily or in divided doses
Maintenance: 2 g once daily</td><td>1 g 1–2 times daily</td><td>1 g at night for 2–3 weeks</td></tr>
<tr><td colspan="4">Olsalazine (oral) – rarely used
• Acute flare: initially 500 mg the first day, increased by 500 mg daily up to 2g daily in divided doses; maximum 1 g three times daily
• Maintenance: 500 mg twice daily</td></tr>
<tr><td colspan="4">Sulfasalazine (oral) – mainly used to treat accompanying joint pain
• Acute flare: 1–2 g four times daily
• Maintenance: 500 mg four times daily</td></tr>
<tr><td>Corticosteroids</td><td colspan="4">Prednisone (oral)
• Acute flare: initially 40 mg daily for at least two weeks, then reduce dose by 5 mg per week</td><td>• Prescribed for acute treatment if an ASA is ineffective at controlling symptoms, or sometimes used initially in patients with severe symptoms
• Commonly used initially for patients with diffuse Crohn's disease or left-sided colonic disease
• Not indicated for IBD maintenance treatment (avoid long-term use)
• Monitor risk of osteoporosis and osteonecrosis with oral corticosteroid use</td></tr>
<tr><td colspan="4">Hydrocortisone acetate (enema)*
• 1 metered application (approximately 90–100 mg) inserted into the rectum 1–2 times daily for 2–3 weeks, then once daily on alternate days</td></tr>
<tr><td rowspan="4">Initiated by a gastroenterologist as required</td><td rowspan="3">Immuno-modulators</td><td colspan="4">Azathioprine (commonly used)
• 2.5mg/kg body weight daily</td><td rowspan="3">• Can be used in pregnancy
• May take 3–6 months to achieve remission
• Serum thiopurine methyltransferase (TPMT) needs to be requested first to identify patients at risk of serious adverse effects and to assess how much azathioprine and mercaptopurine to prescribe
• Three-monthly blood tests are required (initially weekly)</td></tr>
<tr><td colspan="4">Mercaptopurine
• 1–1.5 mg/kg body weight daily</td></tr>
<tr><td colspan="4">Methotrexate
• 15–25 mg together with folic acid 5 mg, once weekly</td><td>• Second-line immunomodulator
• Not suitable in pregnancy due to teratogenic effects</td></tr>
<tr><td>Biologics</td><td colspan="4">Adalimumab (subcutaneous injection)
• Maintenance 40 mg, every two weeks</td><td rowspan="2">• Initial application for Special Authority (SA) is by a gastroenterologist only
• General practitioners may apply for renewal for SA on recommendation of a gastroenterologist
• Do not give live vaccines when using a biologic; administer these at least one month before initiation
• Consider annual influenza vaccine and five-yearly pneumococcal vaccine</td></tr>
<tr><td colspan="4">Infliximab (intravenous)
• Maintenance 5mg/kg body weight, every 8 weeks</td></tr>
</table>

* Hydrocortisone acetate rectal foam (Colifoam) has been out of stock since early 2019. The supplier has advised PHARMAC that resupply is expected mid-2021. An alternative product prednisolone sodium – rectal foam 20 mg per dose (Essential Prednisolone) has been listed on the Pharmaceutical Schedule since 1 October, 2020. Essential Prednisolone is not approved for use in New Zealand and must therefore be prescribed under Section 29 of the Medicines Act. For further information, see: **https://pharmac.govt.nz/medicine-funding-and-supply/medicine-notices/**

Lifestyle advice for patients with IBD

Following diagnosis, primary care has a pivotal role in educating patients about IBD and directing them to resources that may help them better self-manage their condition. Lifestyle changes alone are insufficient to completely control IBD activity but can help reduce the frequency and severity of flares when accompanied by appropriate medicine use (see: "Medicines used in the treatment of IBD").

Smoking cessation. All patients with IBD who smoke should be advised to stop.[1] In patients with Crohn's disease, smoking is associated with worse disease outcomes and they are approximately 30% more likely to require surgery than non-smokers.[13]

Practice point: patients with ulcerative colitis should be advised that smoking cessation sometimes precipitates a flare of disease activity, however, it is important to focus on the broader long-term health benefits of smoking cessation, e.g. a reduced cardiovascular disease risk.

Diet. There is conflicting evidence regarding the role of diet in both ulcerative colitis and Crohn's disease; to date, no single dietary component has been linked to symptom relapse.[14] If a dietary trigger is suspected, however, it is reasonable for the patient to trial avoidance to see if symptoms improve. Patients with IBD should be encouraged to maintain a healthy overall diet, with the International Organisation for the Study of Inflammatory Bowel Diseases now recommending the following emphases:[14]

- **Crohn's disease** – ensure a regular intake of fruits and vegetables (in the absence of symptomatic strictures)
  - **Reduce:** the intake of saturated/trans fats, foods with high levels of emulsifiers, highly processed dairy or foods rich in maltodextrins (e.g. salad dressings, canned soups, sports drinks), foods with high levels of artificial sweeteners
  - **Avoid:** unpasteurised dairy products where possible
- **Ulcerative colitis** – increase consumption of natural sources of omega-3 fatty acids such as salmon or flax/chia seeds
  - **Reduce/avoid:** same foods as for Crohn's disease, as well as potentially avoiding red and processed meat

In addition, if a patient with IBD is overweight, or gains weight as a result of steroid-use, then weight loss should be encouraged to reduce the risk of complications.[3]

Dietitian review should be strongly considered in all patients with IBD, particularly in younger patients as they often restrict their diet excessively in an attempt to control symptoms, leading to malnourishment. Patients with IBD can be referred for publicly funded dietitian support if they experience unintentional weight loss and/or nutrient deficiencies as evidenced by diet history and/or blood tests, e.g. low iron stores, vitamin B12, folate. One technique utilised by dieticians is called Exclusive Enteral Nutrition (EEN), which has been found to be as effective as corticosteroids in inducing remission in children with Crohn's disease (and to a certain extent in adults).[15]

For more information on EEN, see Appendix 4 in **https://media.starship.org.nz/inflammatory-bowel-disease-appendices/Appendices_Aug_2015.pdf.**

Exercise. Studies have demonstrated that weight-bearing exercise can help reduce fatigue in patients with IBD, and may potentially help decrease disease activity.[1, 16] In addition, exercise improves bone health, decreasing the risk of osteoporosis, e.g. in patients taking prolonged courses of corticosteroids.[1]

Psychological coping skills. Depression and anxiety are more common in people with IBD, and while stress itself is not considered a cause of IBD, it can exacerbate symptoms when they do occur.[1] Patients should be equipped with cognitive and behavioural strategies to minimise the impact of IBD on their daily life, and it is important to investigate whether they have emotional support networks in place, e.g. family, friends, community support groups.[1] Although patients are encouraged to accept that they have a chronic incurable illness, it should be emphasised that IBD does not have to dominate their life, and that there are ways to control/minimise stress, and to effectively manage IBD during their normal daily activities and employment.

Practice point: patients often only talk about the impact IBD symptoms have on their life when directly asked. Ask questions early on to initiate a broader discussion around IBD, e.g. "*Has this condition affected your ability to engage in activities you normally enjoy?*"

Surgical management of IBD

Despite optimal medicine use, approximately 60–80% of people with Crohn's disease require a segmental intestinal resection, and 20% of those with ulcerative colitis undergo proctocolectomy for medically refractory disease.[19] The need for surgery, and the type of procedure required, will primarily be directed by the gastroenterologist and colorectal surgeon, but decisions will be informed by evidence from monitoring in primary care.

Indications for surgery in patients with IBD:

- Lack of response or intolerance to standard funded medicines
- Pre-cancerous or cancerous changes in the colon in people with a long history of active IBD (see: "surveillance colonoscopy")
- Crohn's disease – complications such as fistulae, abscesses, perforation, excessive bleeding or stricture leading to obstruction
- Ulcerative colitis – acute complications, e.g. toxic megacolon or haemorrhage

Patients taking a corticosteroid, immunomodulator or biologic medicine prior to surgery have a higher post-operative risk of infection.[15] Therefore, steps should be taken to alleviate infection risk, e.g. pre-operative antibiotics and advising weight loss and smoking cessation if relevant.[19]

Other longer-term aspects of management to consider

Surveillance colonoscopy. Patients with IBD have an increased risk of developing bowel cancer compared with the general population.[21] The mortality rate due to bowel cancer in people with IBD is 10–15%. Therefore, surveillance colonoscopy should be performed after IBD symptoms have been present for eight to ten years, and then repeated every:[21]

- 5 years for patients with a low risk of bowel cancer
- 3 years for patients with an intermediate risk of bowel cancer
- 1 year for patients with a high risk of bowel cancer

N.B. The risk calculation depends on duration and extent of disease, and the severity of inflammation and can change after every colonoscopy.

For more information on bowel cancer risk determinants in patients with IBD, see: **https://www.health.govt.nz/system/files/documents/publications/colorectal-cancer-surveillance-guidance.pdf**

IBD can affect medicine absorption. Changes to the characteristics and composition of the GI tract varies between patients with IBD.[1] In some cases, IBD pathology may substantially influence the transit, absorption and subsequent bioavailability of oral medicines, including those used to treat IBD itself, and those required for managing co-morbidities.[1] In patients with IBD that exhibit a sub-optimal response to oral medicines without an obvious explanation, consult with a pharmacist or gastroenterologist for advice.

Contraception. IBD may influence the suitability of some hormonal contraceptives:[22]

- IBD increases the risk of osteoporosis, and the effect of depot medroxyprogesterone acetate on bone density may be additive. Therefore, an alternative contraceptive that does not affect bone density should be advised.
- The combined oral contraceptive pill (COC) may not absorb as effectively in patients with Crohn's disease with small bowel involvement; avoid COC in patients prone to severe exacerbations requiring hospitalisation

Pregnancy. For women wanting to become pregnant, maintaining optimal control over IBD symptoms generally increases the likelihood of conception, particularly in people with Crohn's disease. Patients should be advised that IBD is associated with a higher risk of pre-term birth and caesarean sections are more common in patients with active disease.[22] Most medicines used for IBD can be safely continued during pregnancy:[1, 23]

- The main exception is methotrexate, which is contraindicated in pregnant women (Table 2); pregnancy should be delayed for at least three to six months after stopping methotrexate
- Biologics such as infliximab and adalimumab can cross the placenta during the first trimester of pregnancy; while these medicines are not thought to harm the fetus, live vaccines are routinely avoided in the infant during the first six months of life if the mother receives biologic treatment due to risk of immunosuppression (however, the evidence regarding this is conflicting)

Prognosis is variable

Both principal forms of IBD have a relapsing-remitting course; the long-term prognosis varies considerably and is dependent on patient characteristics and their tailored treatment plan.

Ulcerative colitis:[24]

- Following diagnosis, approximately 50% of patients experience a flare during the next one to two years
- A small proportion have a single presentation of symptoms followed by no recurrence or perhaps a single flare over the course of decades
- Approximately 1% of patients with ulcerative colitis experience persistently active disease five years after diagnosis

Crohn's disease:[25]

- The course of disease tends to be more variable and less favourable than for ulcerative colitis – prognosis varies based on anatomical location and severity
- Following diagnosis, cumulative relapse rates have been demonstrated to be:
  - 53% at one year
  - 85% at five years
  - 90% at ten years
- Patients requiring systemic steroid treatment for their first flare, or that present with perianal involvement, are more likely to experience a relapse of symptoms later

If surgery is required for either form of IBD, then a colonoscopy after one year – accompanied by visualisation of the surgical anastomosis – can give a more definitive and individualised prognostic outlook.

Leading a fulfilling life with IBD

Although each patient's experience is unique, it is possible to live a fulfilling and productive life despite being diagnosed with IBD, and this should always be a focus in early discussions about the condition.

Crohn's and Colitis New Zealand has prepared a "Living with IBD Handbook", which is a useful resource to enable patients to think positively about their future and identify ways with which they can better self-manage their condition. IBD Passport provides information relating to travel with IBD and is endorsed by the New Zealand Society of Gastroenterology and Crohn's and Colitis New Zealand.

For access to the "Living with IBD Handbook", see: **https://crohnsandcolitis.org.nz/IBD+Handbook**

For access to the "IBD Passport", see: **https://www.ibdpassport.com/**

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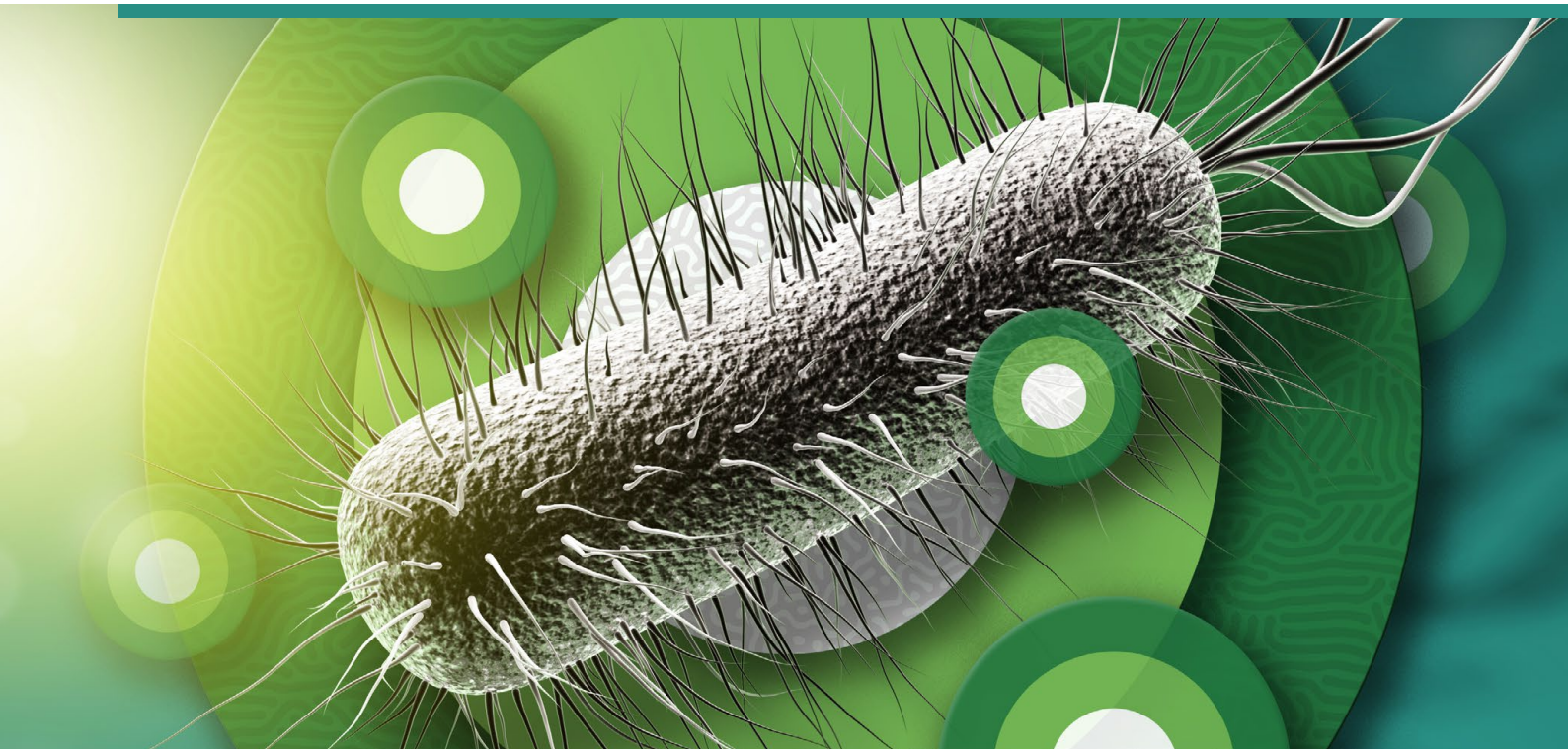


Limiting the use of quinolone antibiotics

Quinolones (e.g. ciprofloxacin, norfloxacin) are associated with increasing antimicrobial resistance and rare, but potentially harmful, adverse effects. Their use should be reserved for specific indications involving serious bacterial infections, in order to protect their effectiveness. There are few situations where quinolones are recommended first-line, such as prostatitis, epididymo-orchitis (if a urinary pathogen is suspected) and severe cases of salmonellosis. Patients prescribed quinolones should be advised about the risk of rare but serious adverse effects, including tendon rupture and aortic aneurysm.

KEY PRACTICE POINTS:

- Reserve for specific indications:
  - Limit use to serious, life-threatening or difficult-to-treat infections, when other antibiotics cannot be used due to allergy, intolerance or antimicrobial resistance
  - Dispensing data show that ciprofloxacin and norfloxacin use has been steadily decreasing since 2015; conversely, moxifloxacin use has more than doubled between 2015 and 2019
- Indications for ciprofloxacin:
  - First-line for the treatment of patients with prostatitis, epididymo-orchitis (if a urinary tract infection pathogen is suspected) and severe cases of salmonellosis
  - Gonorrhoea (if known to be susceptible) and severe cases of shigellosis (if known to be susceptible and unable to take the first-line treatment), *Campylobacter enterocolitis* (second-line) and some eye and ear infections
  - Ciprofloxacin can be considered for the treatment of patients with uncomplicated urinary tract infection that is unresponsive or resistant to a first-line treatment
  - Ciprofloxacin should not be used for pneumococcal pneumonia or travellers' diarrhoea
- Indications for other quinolones:
  - Moxifloxacin is indicated (unapproved) for *Mycoplasma genitalium* infection if first-line treatment with doxycycline followed by azithromycin has failed or there is known macrolide resistance. Moxifloxacin is also an approved treatment for multi-drug resistant tuberculosis.
  - Norfloxacin is no longer recommended for the treatment of patients with uncomplicated urinary tract infection due to the potential for resistance
- Adverse effects of quinolones:
  - These medicines are generally well tolerated, with the most common adverse effect being gastrointestinal disturbance. In rare circumstances serious adverse effects can occur, including tendon rupture, aortic aneurysm rupture or dissection, CNS excitation and seizures, and QT prolongation.
  - Older or frail people are at increased risk of experiencing adverse effects with quinolones; ciprofloxacin and norfloxacin dose adjustment is required for patients with impaired renal function

Quinolones: an overview

Quinolones are a class of broad-spectrum antibiotics that inhibit bacterial DNA synthesis. The addition of a fluorine atom to a quinolone forms a subset of medicines referred to as fluoroquinolones, which have enhanced antimicrobial activity. Fluoroquinolones available in New Zealand include:[1]

- Ciprofloxacin (tablets, eye drops, ear drops* and solution for IV infusion)
- Norfloxacin (tablets)
- Moxifloxacin (tablets and solution for IV infusion)
- Levofloxacin (tablets [section 29, unapproved medicine])

* Formulated with hydrocortisone; indicated for the treatment of otitis externa if *Pseudomonas* is suspected

N.B. Prescribing restrictions, endorsements and Special Authority criteria apply, see Table 1 for details.

Quinolones are most active against Gram-negative bacteria

Quinolones are very active against aerobic Gram-negative bacilli and cocci, including *Enterobacteriaceae, Pseudomonas aeruginosa, Haemophilus influenzae, Moraxella catarrhalis* (*Branhamella catarrhalis*) and *Neisseria gonorrhoeae*. They are generally less active against Gram-positive organisms such as staphylococci and much less active against streptococci such as *Streptococcus pneumoniae*.[2] Quinolones are generally not effective against anaerobic organisms.

Moxifloxacin is a later generation quinolone and has greater activity against Gram-positive organisms and atypical organisms than ciprofloxacin or norfloxacin, and is also active against anaerobes.[2] Many treatment resistant *Streptococcus pneumoniae* isolates are susceptible to moxifloxacin, although it is not funded for this indication. Moxifloxacin should not be considered effective against *Pseudomonas aeruginosa*. While it is not first-line, it does have activity against susceptible methicillin-resistant *Staphylococcus aureus*.[3]

There are few indications for use in primary care

A restrictive approach to the use of quinolones is recommended as community prescribing of quinolones significantly contributes to antimicrobial resistance (see: "Quinolone resistance is increasing"). Ideally, quinolones should be reserved for serious, life-threatening or difficult-to-treat infections, when other antibiotics cannot be used due to allergy or intolerance, or when the pathogen is resistant to alternative antimicrobial agents (see Table 1).

For further information on prescribing quinolones for individual conditions as per Table 1, including dosing and regimen recommendations, see: **https://bpac.org.nz/antibiotics/guide.aspx**

Clinical scenarios where ciprofloxacin is not recommended

Ciprofloxacin should not be used for:

- Pneumococcal pneumonia – it does not cover *Streptococcus pneumoniae* adequately
- Repeat courses for chronic prostatitis if bacterial involvement not confirmed – chronic prostate pain is frequently not due to infection
- Travellers' diarrhoea – antibiotic treatment is not typically required as the infection is usually self-limiting and may be caused by bacteria, viruses or protozoa. Patients with severe or persistent symptoms should be discussed with an Infectious Diseases Physician or Clinical Microbiologist to decide on an appropriate treatment regimen, depending on the causative pathogen. Azithromycin is often a recommended choice.
- Diverticulitis – anecdotally, patients are often treated with ciprofloxacin, however, the recommended first-line regimen is trimethoprim + sulfamethoxazole and metronidazole; amoxicillin clavulanate is an alternative.[4]

Ciprofloxacin is generally not recommended for pyelonephritis, although it is used occasionally. Trimethoprim + sulfamethoxazole is first-line; amoxicillin clavulanate and cefalexin are alternatives.[4]

N.B. Norfloxacin should not be used for pyelonephritis as it has poor tissue penetration and is no longer recommended for uncomplicated urinary tract infection. Some DHBs have excluded norfloxacin from their formularies as it is no longer considered appropriate due to resistance and safety concerns.

Key considerations when prescribing quinolones

Quinolones are generally well tolerated, with the most common adverse effects resulting from gastrointestinal disturbance, as with most antibiotics (Table 1). Less frequently, people using quinolones may experience central nervous system effects (e.g. headache, insomnia, dizziness, anxiety, restlessness, tremor), crystalluria*, rash or photosensitivity.[18]

In rare circumstances, serious adverse effects can occur, including tendinitis and tendon rupture, progression or rupture of an aortic aneurysm or aortic dissection, QT prolongation, retinal detachment, CNS excitation and seizures (see: "Tendinitis and tendon ruptures are a rare adverse effect" and "Caution is required when prescribing quinolones in some patients").[2,19] The risk of serious adverse effects seems to be greater with later generation quinolones (i.e. moxifloxacin) than with earlier generations (i.e. ciprofloxacin and norfloxacin).[18]

* The formation of crystals in the urine due to poor hydration and urine alkalinity; the condition is usually benign, but there have been reported cases of renal failure associated with crystal precipitation [20, 21]

Table 1. Indications for quinolones in primary care. N.B. There are no indications for norfloxacin in primary care.[1, 4–8]

Ciprofloxacin	Moxifloxacin
■ **Epididymo-orchitis** – first-line if a UTI pathogen is suspected ■ **Prostatitis** – first-line for acute and chronic bacterial prostatitis ■ **Otitis externa with secondary infection** – only if *Pseudomonas* is suspected* ■ **Chronic suppurative otitis media** [unapproved indication]† ■ **Bacterial keratitis** or **severe bacterial conjunctivitis** resistant to chloramphenicol† ■ **Gonorrhoea** – only if isolate is known to be susceptible and an alternative to first-line treatment is required ■ **Chronic relapsing UTI in adults** – fourth-line if treatment with nitrofurantoin, trimethoprim or cefalexin has failed or the organism is not sensitive‡ ■ **Salmonella enterocolitis** – first-line for severe infection, those who are immunocompromised or have prosthetic vascular grafts ■ ***Salmonella typhi*** and ***S. paratyphi*** – if isolate is known to be susceptible ■ ***Campylobacter enterocolitis*** – second-line after erythromycin for severe or prolonged infection, or those at high risk of complications ■ **Shigellosis** – only if severe and isolate is known to be sensitive ■ **Other indications** include invasive *Pseudomonas* infections, *Legionella* pneumonia, bone and joint infections and prophylaxis of meningococcal disease, when no alternative is available	■ ***Mycoplasma genitalium*** **urethritis**** [unapproved indication] – first-line is doxycycline (to reduce bacterial load) followed by either azithromycin or moxifloxacin (if macrolide resistant or treatment with azithromycin has failed). Neither azithromycin nor moxifloxacin are recommended first-line.

* Ear drops formulated with hydrocortisone (not funded)

† Eye drops are subsidised by endorsement when prescribed for the treatment of bacterial keratitis or severe bacterial conjunctivitis resistant to chloramphenicol; or for the second-line treatment of chronic suppurative otitis media (unapproved indication).

** Moxifloxacin can be prescribed fully funded with Special Authority approval for the treatment of *M. genitalium* infection (unapproved indication). Applications are to be made by a sexual health specialist or on their recommendation. N.B. A similar regimen is likely to be appropriate for persistent cervicitis or severe pelvic inflammatory disease caused by *M. genitalium* infection.

‡ Consider the underlying cause of relapsing UTI, e.g. a prostatic abscess or renal tract abnormality

For further information on *Mycoplasma genitalium*, see: **https://bpac.org.nz/2019/mycoplasma-genitalium.aspx**

Patients should be advised about the risks so that they can prevent or minimise the impact of any adverse effects if they occur.

Advise patients to:

- Increase fluid intake to reduce the risk of crystalluria
- Apply sunscreen or cover exposed areas of skin when outdoors to avoid a photosensitivity reaction
- Stop taking the quinolone and consult with a health professional if tendon pain or swelling occurs, or symptoms of neuropathy, e.g. pain, burning, tingling, numbness or weakness
- Report any neurological symptoms, e.g. confusion, anxiety, restlessness, to a health professional

N.B. Prescribers should report adverse reactions to the Centre for Adverse Reactions Monitoring (CARM). Reports can be made through your Adverse Reaction Reporting tool in your patient management system or via a variety of other methods. For further information, see: **https://nzphvc.otago.ac.nz/reporting/**

Patient information leaflets are available from the New Zealand Formulary: **https://www.nzf.org.nz/nzf_70421**

Caution is required when prescribing quinolones in some patients

Many of the adverse effects associated with quinolones occur more frequently in people with pre-existing risk factors, or in certain at-risk groups, including older people and those with epilepsy.

Older people

Quinolones should be used at the lowest effective dose in older people for as short a duration as clinically possible, to reduce the development of resistance and adverse effects. Renal function declines consistently with age and ciprofloxacin and norfloxacin doses need to be reduced accordingly to avoid adverse effects. For example, an appropriate oral dose for ciprofloxacin in renal impairment is 250–500 mg, twice daily, if eGFR is 30–60 mL/minute/1.73 m^2 or once daily, if eGFR < 30 mL/minute/1.73 m^2.[1]

Many antibiotic classes are associated with adverse CNS effects; these appear to be more common with quinolones than other systemic antimicrobials and are of particular concern in older people.[24] Some adverse CNS effects in older people may be attributed to ageing, acute illness, other conditions or other medicines so it is important to consider quinolone use when CNS symptoms are reported.

Tendinitis and tendon ruptures are a rare adverse effect

A number of toxicological studies have confirmed that quinolones damage the collagen within tendons, which on rare occasions can result in tendinitis and tendon rupture, particularly affecting the Achilles tendon with bilateral involvement possible. This can occur even after a single dose of quinolone and the risk can persist for months.[22] Tendon rupture has been reported within 48 hours of starting treatment, however, cases have also been reported several months after stopping treatment.[22]

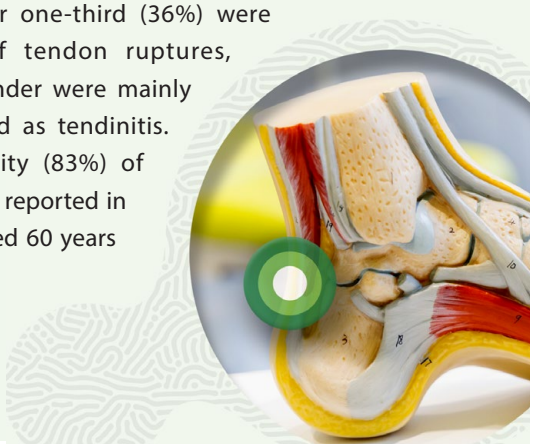
Risk factors for tendon disorders associated with the use of quinolones include:[1, 19, 23]

- Age over 60 years
- Concomitant oral corticosteroid treatment
- Chronic kidney disease
- Previous kidney, heart or lung transplant
- Prior history of tendon damage

Although this adverse effect is rare (estimated incidence rate 0.14% to 0.40%),[22] it is important to remember that:[1]

- Quinolones are contraindicated in patients with a history of tendon disorders related to previous quinolone use
- If tendinitis is suspected, the quinolone should be discontinued immediately

Between 2007 and 2012, CARM received 53 reports of tendon disorders associated with quinolone use.[14] Over one-third (36%) were reports of tendon ruptures, the remainder were mainly categorised as tendinitis. The majority (83%) of cases were reported in people aged 60 years and over.



People with epilepsy or a history of CNS disorders

Quinolones should be used with caution in people at increased risk of seizures, those with CNS disorders or in patients concurrently using medicines which may lower the seizure threshold, e.g. bupropion, due to the potential for adverse CNS effects.[25] The risk of seizures, although very rare, may be increased with concomitant NSAID treatment.[25]

People at risk of aortic aneurysm or dissection

A similar mechanism relating to collagen degradation with quinolone treatment that leads to tendon rupture (see: "Tendinitis and tendon ruptures are a rare adverse effect") may occur in the wall of the aorta, contributing to an approximately two-fold increase in the risk of progression or rupture of an aortic aneurysm or aortic dissection within 60 days following treatment.[15, 26] This is a rare effect and as of March 2019, no cases were reported in New Zealand.[15]

Risk factors include:[15, 19, 27]

- Family history of aneurysm
- Pre-existing aortic aneurysm or dissection
- Certain pre-disposing conditions, e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease
- Atherosclerosis
- Hypertension
- Age > 65 years

Quinolones should only be prescribed to people with these risk factors if there are no suitable alternatives and the benefits of treatment outweigh the potential harms. Patients should be advised to seek urgent medical advice if they develop sudden-onset, severe chest, abdominal or lower back pain during or following treatment.[19]

Medicine interactions

Quinolones can interact with a number of other medicines, such as those that reduce seizure threshold, prolong the QT interval, warfarin and medicines metabolised by common pathways in the liver. For further details on medicines that interact with quinolones, refer to the NZF Stockley's interactions checker: **https://www.nzf.org.nz**

Quinolones should be used cautiously in patients taking warfarin as these medicines may interact to increase the international normalised ratio (INR) and cause severe bleeding. If a quinolone is the most appropriate treatment option, monitor the INR three days after initiating antibiotic treatment.[1]

Other at-risk groups

Caution is also required with quinolone use in people with:[1]

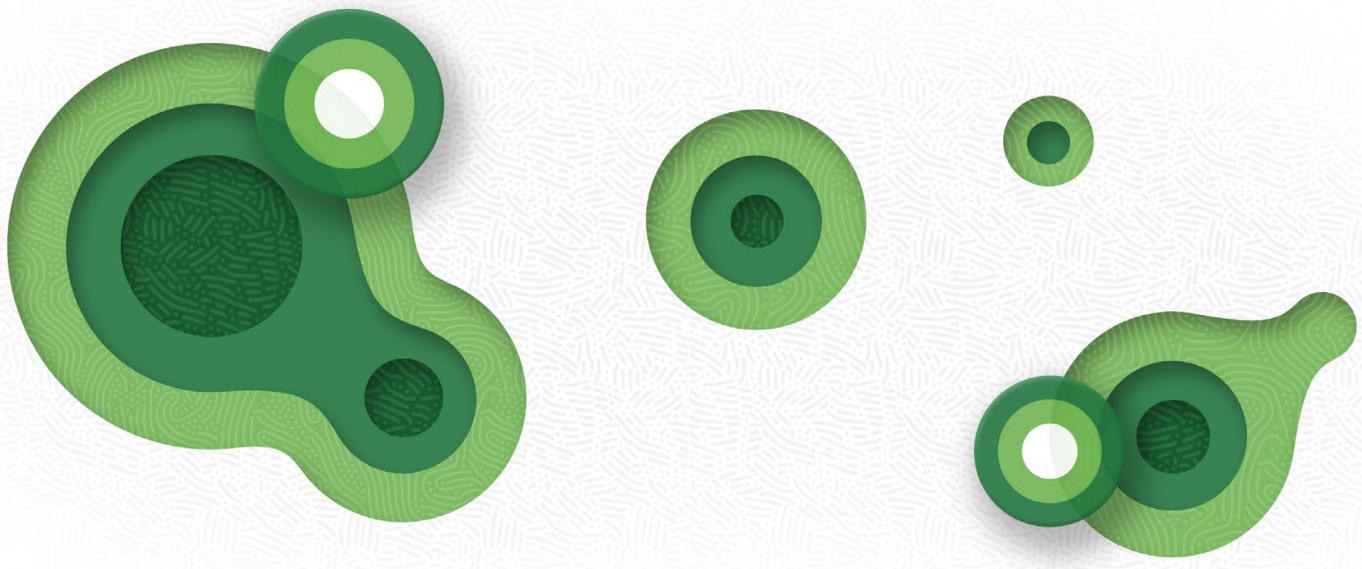
- Diabetes – glucose levels may be increased or decreased
- Myasthenia gravis – symptoms may be exacerbated
- G6PD deficiency – increased risk of haemolytic anaemia

Quinolones are generally not used in children

Quinolones are not recommended for use in people aged under 18 years as they have been associated with arthropathy and damage to immature cartilage of weight-bearing joints in animal studies.[1] There are some specific circumstances, such as pseudomonal infections associated with cystic fibrosis, where the short-term use of ciprofloxacin may be justified in children.[28]

Quinolones should be avoided in pregnancy and while breastfeeding

All quinolones should be avoided in pregnancy as they have been shown to cause arthropathy in animal studies.[1] There are limited data available on the safety of quinolone use while breastfeeding. The manufacturers recommend avoiding use as small amounts are detected in the breast milk.[1]



Quinolone resistance is increasing

Antimicrobial resistance to quinolones is prevalent globally, and includes both Gram-negative and Gram-positive strains. In New Zealand, resistance has been shown in:

- *Haemophilus influenzae* – susceptibility testing of 83 isolates by the Institute of Environmental Science and Research (ESR) in 2017 found 2.4% were resistant to ciprofloxacin[9]
- *Neisseria gonorrhoeae* – susceptibility testing of 425 isolates by the ESR in 2015 found 32% were resistant to ciprofloxacin[10]
- *Mycoplasma genitalium* – studies conducted in 2017 and 2020 reported 19–27% of 115 and 81 *M. genitalium* isolates, respectively, had mutations associated with increased resistance to quinolones[11,12]
- *Shigella* – a 2018 study reported 23% of 263 *Shigella* isolates were resistant to ciprofloxacin and norfloxacin[13]

Ciprofloxacin and norfloxacin use in New Zealand is decreasing

Dispensing data from the last five years show that ciprofloxacin and norfloxacin use has been steadily decreasing (Figures 1 A and B). Increased awareness of the harms of quinolone treatment, as well as education on rational use, may help to explain this prescribing trend. There have also been changes to funding endorsement for norfloxacin. Medsafe has published two Prescriber Updates on quinolones since 2012, highlighting the risks of tendon rupture and aortic aneurysm or dissection.[14,15] In 2016, the United States Food and Drug Association revised the warnings for quinolones due to the potential for disabling and potentially permanent adverse effects.[16] In 2018, several news media articles on the use and safety of quinolones were published in New Zealand.

In most DHBs, ciprofloxacin and norfloxacin dispensing decreased by 25–50% between 2015 and 2019 (Figure 2).[17] The only DHB without a decrease in ciprofloxacin and norfloxacin

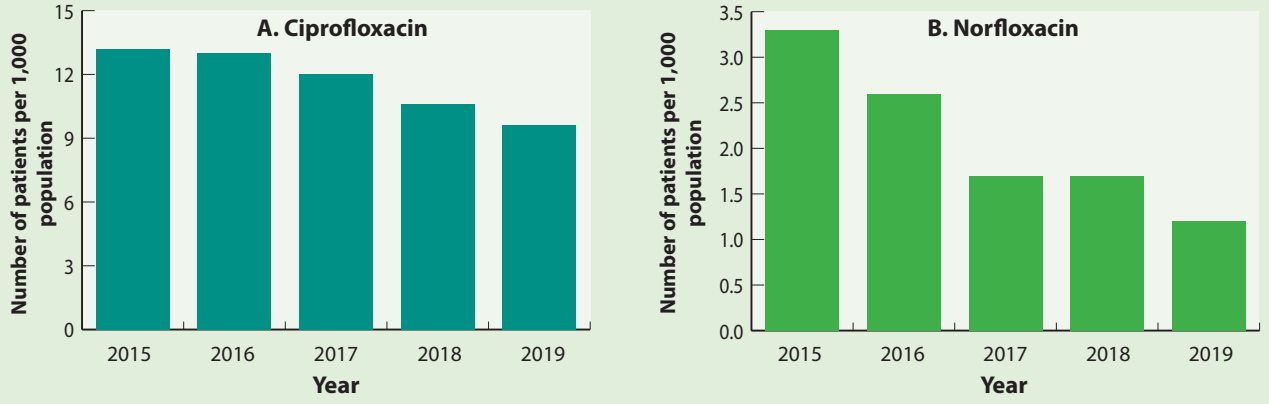


Figure 1 A and B. Number of patients (per 1,000 enrolled patients) dispensed ciprofloxacin (A) or norfloxacin (B), 2015–2019. Note the different scale on the Y axes.

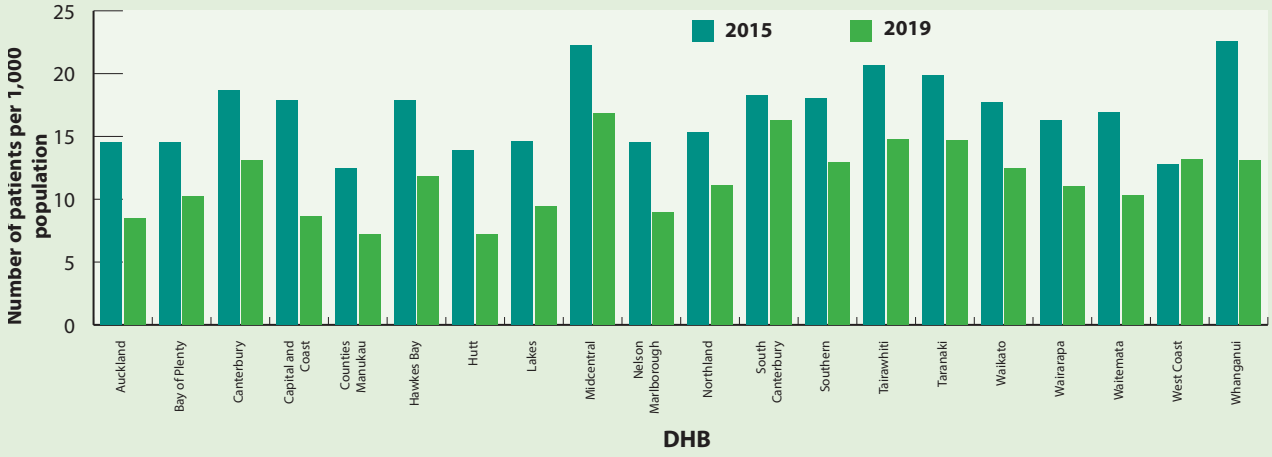


Figure 2. Number of patients (per 1,000 enrolled patients) who were dispensed ciprofloxacin or norfloxacin in 2015 and 2019, by DHB.

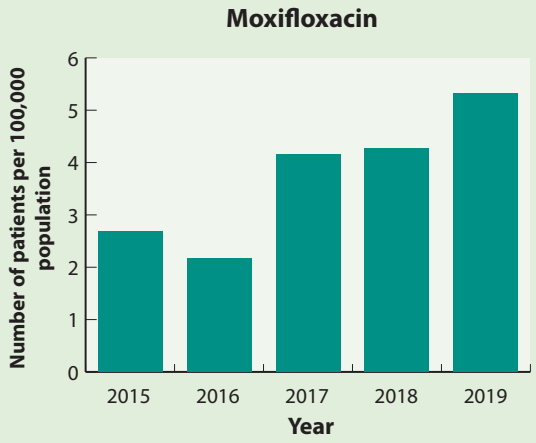
dispensing was West Coast. In 2019, ciprofloxacin and norfloxacin use was highest in Midcentral DHB (17 people per 1,000 population) and lowest in Hutt and Counties Manukau DHBs (7 people per 1,000 population).

Moxifloxacin use is increasing, but total numbers are still small

Moxifloxacin is funded with Special Authority approval for active tuberculosis, *Mycoplasma genitalium* infection and penetrating eye injury. The majority of moxifloxacin prescribing for these indications will occur in secondary care; only applications for *M. genitalium* can be made by a primary care clinician, but this must be on the recommendation of a sexual health physician. Moxifloxacin use more than doubled between 2015 and 2019, however, the total number of patients dispensed moxifloxacin is still very low (i.e. 251 people in total were dispensed moxifloxacin in 2019) (Figure 3). Moxifloxacin dispensing increased in most DHBs between 2015 and 2019 (Figure 4). The highest dispensing rate in 2019 was in Taranaki DHB (17 people per 100,000 population). Possible reasons for this increase include:

- Treatment of infections caused by multi-resistant *S. pneumoniae*
- Increased awareness and laboratory detection of *M. genitalium* infection as a cause of urethritis, cervicitis and pelvic inflammatory disease
- An outbreak of tuberculosis where first-line treatments were inappropriate due to resistance or intolerance

Figure 3. Patients dispensed moxifloxacin (per 100,000 enrolled patients), 2015–2019. Note the scale on the Y axis has been adjusted to represent the comparatively small population of patients dispensed moxifloxacin.



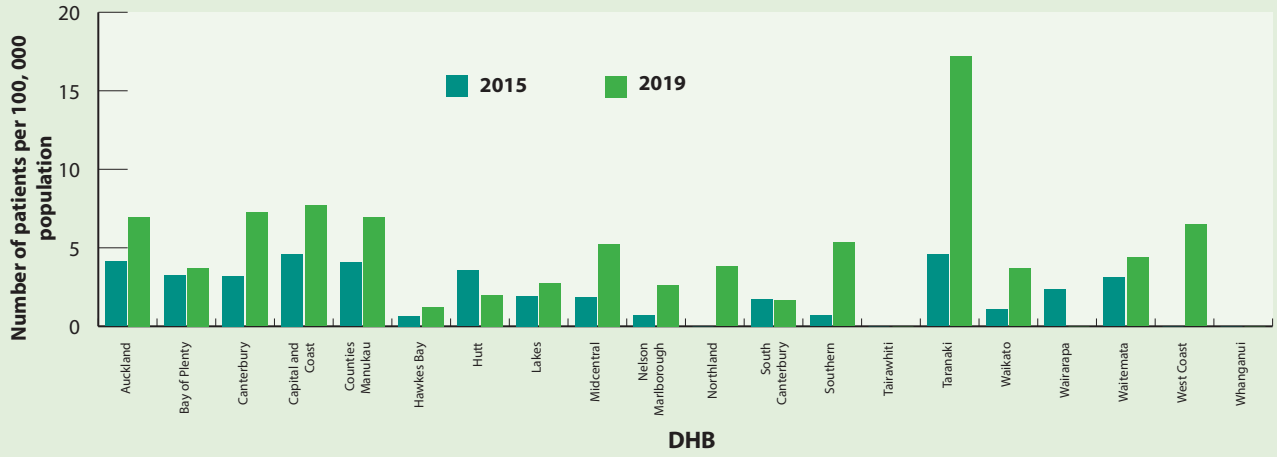


Figure 4. Number of patients (per 100,000 enrolled patients) who were dispensed moxifloxacin in 2015 and 2019, by DHB.

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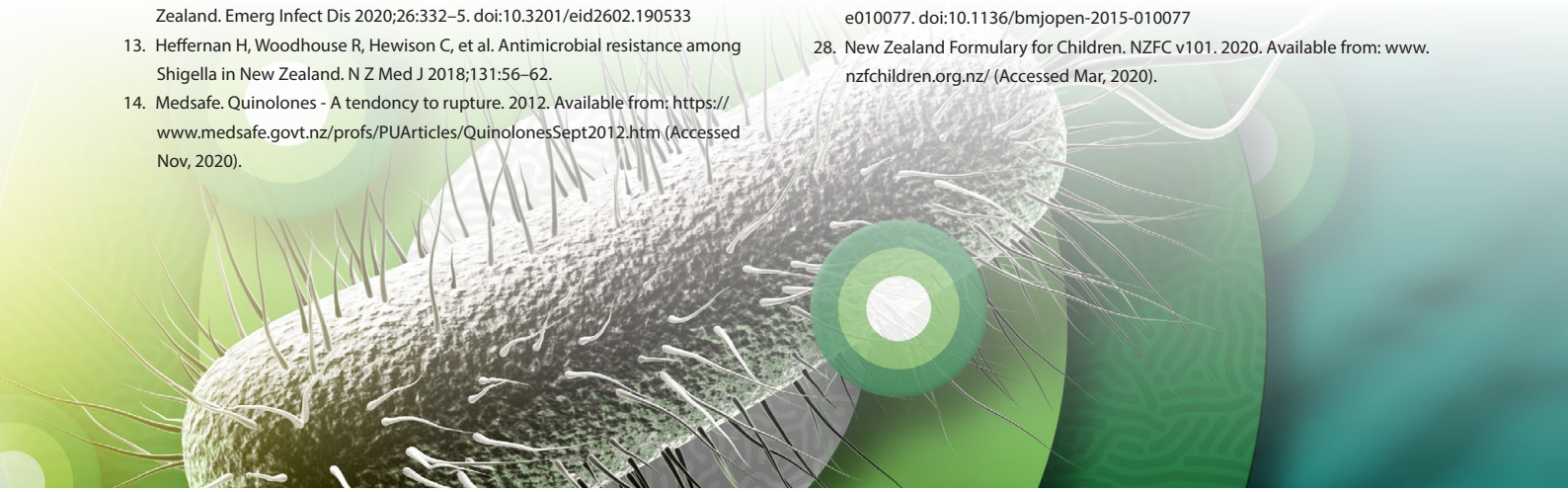
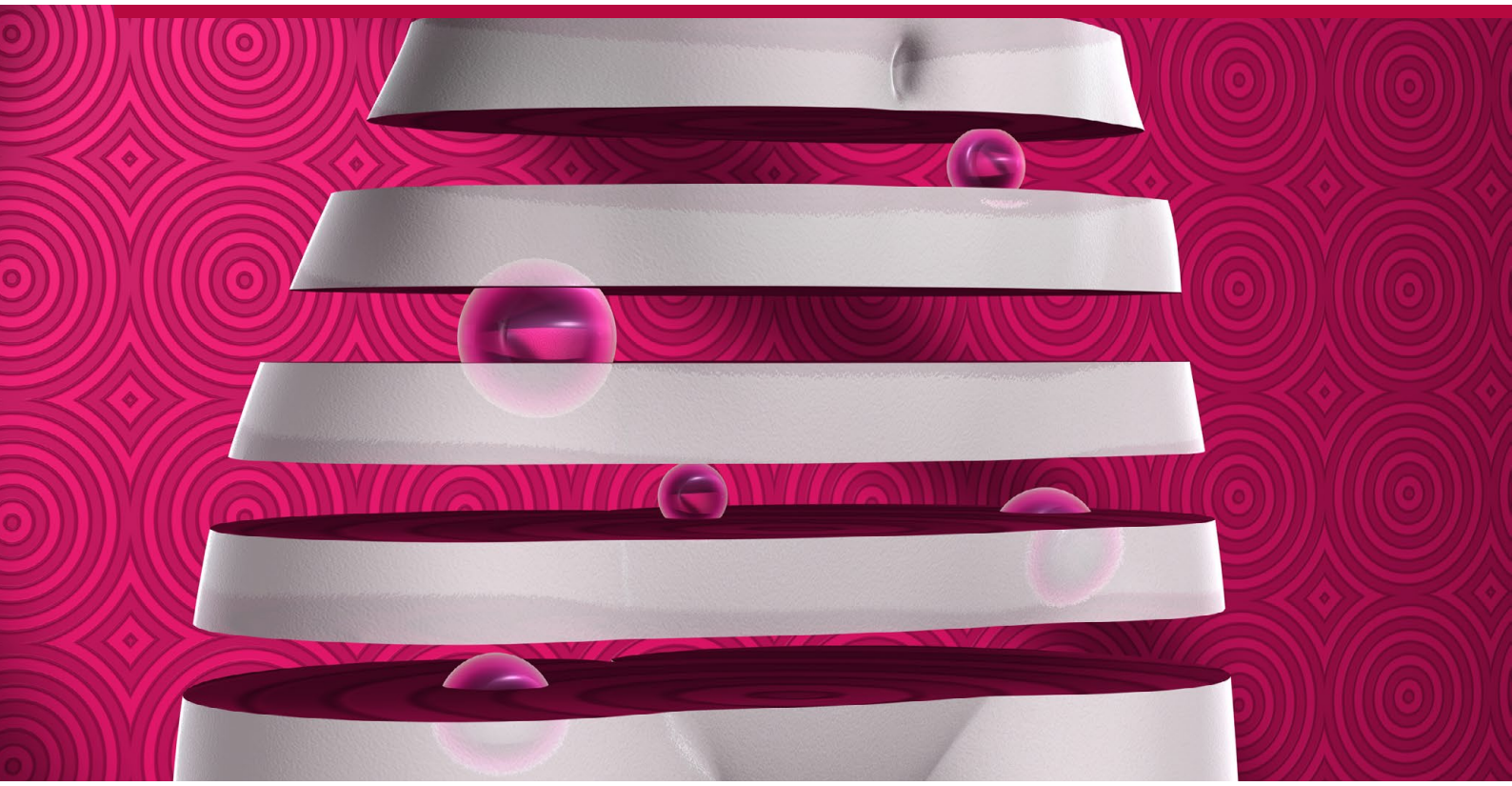




Endometriosis: diagnosis and management

Endometriosis is characterised by the presence of endometrial-like tissue outside the uterine cavity, causing mainly cyclical symptoms and, often, reduced fertility. A clinical diagnosis can be made based on the patient's symptoms and evaluation of risk factors, although laparoscopy is required for definitive diagnosis. Medical management involves the hormonal suppression of endometriotic lesions, with analgesia as required. Surgical excision or ablation of endometriotic tissue is often necessary.

KEY PRACTICE POINTS:

- Endometriosis is estimated to affect 10–15% of reproductive-age women and is a common cause of reduced fertility and pelvic pain
- Endometriosis can be classified as superficial peritoneal lesions, ovarian endometriomas (cysts filled with endometriosis) or deep infiltrating endometriosis. Rarely, endometriosis can occur outside of the pelvis.
- Risk factors for endometriosis include family history, short menstrual cycles (i.e. more frequent menstruation), longer-than-normal menstruation, early menarche, low body mass index, nulliparity
- The most common symptom of endometriosis is pelvic pain. Symptoms are usually cyclical and include dysmenorrhoea, dyspareunia, dysuria, dyschezia, bloating and abdominal pain. Some women may be asymptomatic; difficulty conceiving may be the first presentation with undiagnosed endometriosis.
- Clinical examination (pelvic and/or abdominal) is primarily for the purpose of differential diagnosis; many women with endometriosis have normal examination findings
- Transvaginal and/or abdominal ultrasound imaging is recommended. However, a normal ultrasound does not exclude a diagnosis of endometriosis.
- Hormonal treatment is often first-line for those with endometriosis who do not wish to conceive in the near future, and analgesics if required. Options include progestogen-only treatment (various formulations available) or combined oral oestrogen + progestogen treatment (i.e. a combined oral contraceptive).
- Surgical treatment may be indicated if hormonal treatment is ineffective, not tolerated, contraindicated or not wanted

Endometriosis: a challenging diagnosis

Endometriosis is defined as an inflammatory disease characterised by lesions of endometrial-like tissue outside the uterus that is associated with pelvic pain and/or reduced fertility.[1] The condition generally has three distinct manifestations (also see: "The terminology of endometriosis"):[2]

1. **Superficial peritoneal lesions** – endometrial lesions form on the peritoneum and may penetrate tissue up to 5 mm below the peritoneal surface
2. **Ovarian endometriomas** – cystic masses caused by the growth of endometrial tissue within the ovary
3. **Deep infiltrating endometriosis** – lesions penetrating tissue deeper than 5 mm below the peritoneal surface (e.g. uterosacral ligaments) or lesions that infiltrate the muscularis propria of organs near the uterus (e.g. bladder, intestine, ureter)

Although rare, endometriosis can also occur outside of the pelvis, e.g. pleura, diaphragm, umbilicus.[2, 3]

The clinical presentation of women* with endometriosis varies widely. Some may be completely asymptomatic (and therefore not aware of the condition) while others will have chronic pelvic pain, dysmenorrhoea, dyspareunia and dyschezia.[4] As endometriotic lesions are hormonally-responsive, symptoms will usually be cyclic, worsening at the time of menstruation. During periods of anovulation, such as pregnancy, lactation, menopause and hormone-induced amenorrhoea, symptoms are usually reduced or eliminated. Endometriosis can have a significant effect on female fertility, and many women with undiagnosed endometriosis may first present with difficulty conceiving.

Endometriosis is estimated to affect approximately 10–15% of women of reproductive-age, and as many as half of all women with reduced fertility and 70–90% of women with chronic pelvic pain.[4] The peak incidence of endometriosis is thought to be in women aged 25–35 years.[5, 6] Endometriosis is less common in younger females and post-menopausal women.[7] Endometriosis is also possible in males taking high-dose oestrogen, although this is extremely rare.[8] The exact prevalence of endometriosis in New Zealand, overall and by ethnicity, is not known.

* The term "women" is used to describe the patient population who are most likely to present with endometriosis, however, we acknowledge that this may not reflect the identity of the patient; adolescents, transgender boys or men, and non-binary individuals may present with endometriosis.

Risk-factors for endometriosis

Risk factors for endometriosis include:[2, 4]

- A first-degree female relative (mother or sister) with endometriosis
- Shorter-than-normal menstrual cycle (< 27 days)
- Longer-than-normal menstruation (> five days)
- Low body-mass index
- Early menarche
- Nulliparity
- Müllerian anomalies – abnormal anatomy that arises during the formation of parts of the female reproductive organs
- Outflow obstructions, e.g. cervical stenosis, a transverse vaginal septum or an imperforate hymen

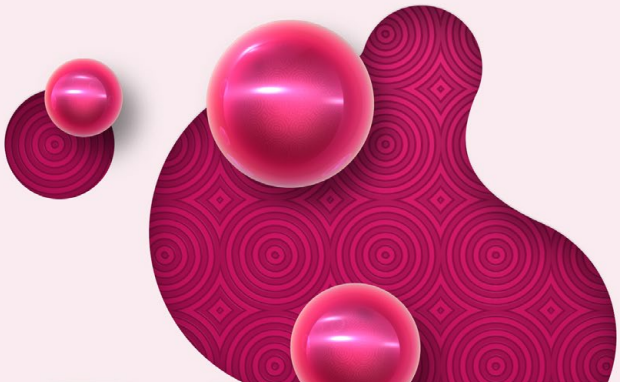
The terminology of endometriosis

Endometriotic lesion – Lesions that occur when endometrial-like tissue exists outside of the uterus. Bleeding may occur from these lesions at the time of menstruation.

Endometrioma – An oestrogen-dependent lesion that is usually enlarged and filled with old blood. When they occur in the ovaries they are often referred to as chocolate cysts.

Endometriotic adhesion – Internal scar tissue that can bind organs and tissues together, causing dislocation and pain. The fallopian tubes, uterus, ovaries, bowel and bladder are the most commonly affected tissues.

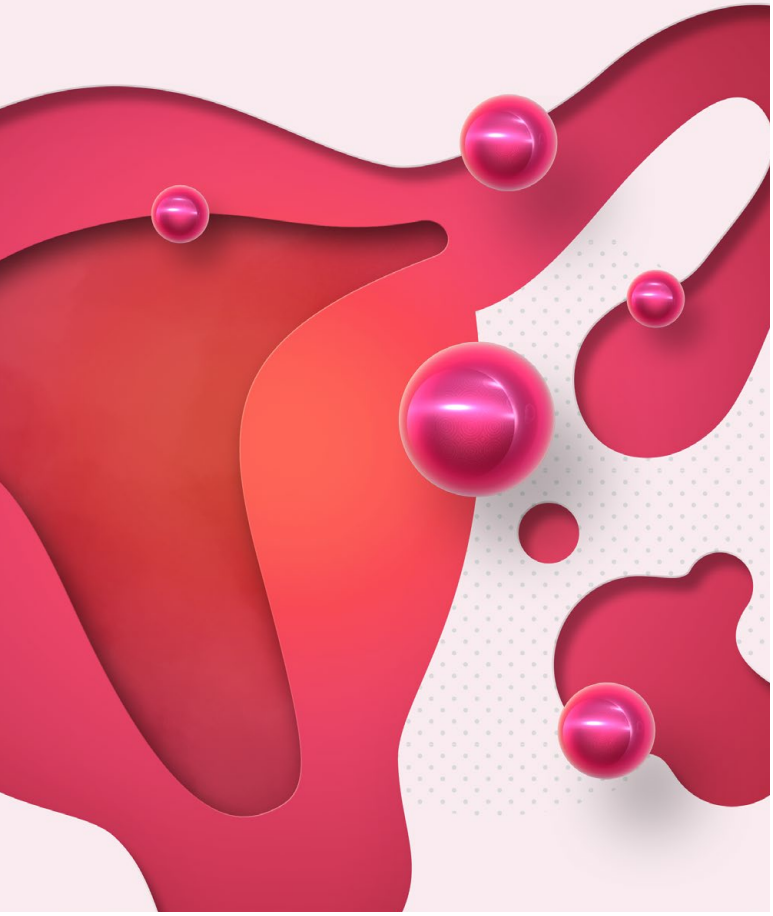
Endometrial stromal nodule – An uncommon, non-infiltrative, confined growth of endometrial stromal cells, which can develop into a rare type of cancer; an endometrial stromal sarcoma, which frequently metastasises.



The cause of endometriosis is unknown

The pathology of endometriosis is not well understood. Retrograde menstruation, where menstrual fluid flows back up the fallopian tubes and into the peritoneal cavity, is one proposed mechanism.[4] Endometrial cells are thought to move with the fluid, possibly through the lymphatic and vascular network. The cells deposit in various tissues, seeding and developing into endometriotic lesions and endometriomas. When this occurs, internal bleeding and inflammation can lead to fibrosis and adhesion development, which in turn contributes to the symptoms and the physical distortion of pelvic anatomy that is seen in women with more severe endometriosis. However, retrograde menstruation is estimated to occur in approximately 90% of women, while only a small proportion will go on to develop endometriosis.[4] Therefore, other factors, such as hormonal, inflammatory or immunologic factors may determine whether lesions implant and persist in the pelvic cavity.[4]

Other postulated mechanisms include endometriosis lesions arising from Müllerian remnants that did not properly differentiate or migrate during fetal development, or from circulating blood cells that differentiate into endometrium-like tissue.[4]



Making a diagnosis of endometriosis

Diagnostic laparoscopy is required to make a definitive diagnosis of endometriosis, this is only indicated, however, if surgical treatment is to occur concurrently.[4, 9] Therefore, health professionals often rely on a presumptive diagnosis, based on history, symptoms and risk factors, to guide management decisions. Timely diagnosis and initiation of medical management of endometriosis is important in reducing avoidable pain and discomfort, improving quality of life and managing fertility. However, diagnosis can be challenging as symptoms are often non-specific, clinical signs on examination are limited, laboratory testing is not helpful and imaging is often of only limited benefit.[2, 4] On average, a delay of seven years between the development of symptoms and diagnosis of endometriosis has been reported, which impacts significantly on the patient's quality of life.[4]

Symptoms are non-specific and common

Approximately one-third of women with endometriosis will be asymptomatic. The most common symptomatic presentation is cyclical pelvic pain.[2] Other common symptoms include:[4, 9, 10]

- Severe dysmenorrhoea
- Lower abdominal or back pain
- Dyspareunia
- Dysuria
- Dyschezia
- Visceral pain during exercise
- Heavy menstruation or pre-menstrual spotting (may also indicate co-existing adenomyosis – see sidebar next page)
- Bloating
- Lethargy
- Constipation
- Reduced fertility

Rarely, endometriotic lesions can occur outside of the abdominal cavity, such as in the lungs, and can cause pain and other symptoms, e.g. pneumothorax or haemoptysis, coinciding with the menstrual cycle.[3] Bowel obstruction secondary to endometriotic adhesions can also occur.

Acute exacerbations of pain, fever, or very rarely, ascites may occur due to chemical peritonitis following leakage of blood from an endometrioma.[3]

Best practice tip: If endometriosis is suspected but there is insufficient time in the consultation to conduct a full history and examination, arrange a follow up appointment and provide the patient with a pelvic pain questionnaire/menstrual diary to fill out and bring with them. An example diary is available from: **https://www.healthinfo.org.nz/patientinfo/45856.pdf**

Clinical examination may be helpful to rule out other conditions

Although women with endometriosis may have normal examination findings, abdominal and pelvic examination should be offered if endometriosis is suspected, primarily for the purpose of differential diagnosis (see below). Diffuse pelvic or posterior fornix tenderness, palpable pelvic masses, or visible vaginal endometriotic lesions are sometimes present in women with endometriosis.[9] Pelvic examination may not be appropriate for those who have never been sexually active.

Laboratory tests and imaging are of limited benefit

There is no laboratory test that can reliably identify endometriosis.[4] Investigation of full blood count, ferritin, thyroid stimulating hormone, urine pregnancy test, urinalysis, C-reactive protein and renal function may be useful in the differential diagnosis. Vaginal and endocervical swabs may be indicated if the history suggests potential risk of a sexually transmitted infection (STI).

Pelvic ultrasound imaging that includes a transvaginal ultrasound (if the patient consents) is recommended.[10] However, a normal ultrasound does not exclude a diagnosis of endometriosis as lesions may not be visible on the scan, depending on the stage of disease.[10]

Differential diagnoses

Women with endometriosis often present with diverse, non-specific symptoms, and other possible diagnoses should always be considered.

Acute symptoms caused by STIs, urinary tract infections and pelvic inflammatory disease often mimic endometriosis, however, given the chronic nature of endometriosis, it is likely that these conditions can be ruled out early.

Some long-term conditions have symptoms that overlap or co-exist with endometriosis and it can be more difficult to rule these out. Differential diagnoses that should be considered in women with pelvic pain include diverticulitis, irritable bowel syndrome, uterine fibroids, urinary tract stones and interstitial cystitis.[11, 12]

Generally, presentation and patient history will shift the balance of probabilities for a diagnosis, e.g. uterine fibroids are more common in an older age-group. However, some conditions will be nearly impossible to rule out until laparoscopy is performed (e.g. adenomyosis – see: "Consider adenomyosis in women presenting with endometriosis symptoms") or a therapeutic trial of treatment is undertaken. Always consider the possibility of other co-existing pathologies including pelvic infection and bowel conditions. In addition, in a small number of women, uterine and Müllerian abnormalities, both of which can be risk-factors for endometriosis, may be present and complicate diagnosis and treatment.

The Raising Awareness Tool for Endometriosis (RATE), a quick-to-use electronic resource for health professionals and patients to help identify and assess endometriosis and associated symptoms, is available from the Royal Australian and New Zealand College of Obstetricians and Gynaecologists: **https://ranzcog.edu.au/womens-health/patient-information-guides/other-useful-resources/rate**

When should a patient be referred for further assessment?

The management of suspected endometriosis depends on the patient's age, desire for fertility, the degree of pain and other symptoms, co-morbidities, the impact on their capacity to work and their quality of life. Generally, a three- to six-month therapeutic trial with hormonal treatment (see below) can be used to manage the symptoms and help strengthen a clinical diagnosis. However, this is not appropriate in many instances, e.g. women wishing to conceive in the near future, those who experience adverse effects with hormonal medicines, have contraindications to their use to or do not wish to use them.

Consider adenomyosis in women presenting with endometriosis symptoms

Adenomyosis occurs when endometrial-like tissue, is present within the muscle layer of the uterus (as opposed to endometriosis which occurs outside the uterine cavity). Adenomyosis is a heterogeneous disease that may present in the myometrium as diffuse, focal or, rarely, cystic. It is usually found in women in an older age group and often after childbirth.[13, 14]

Adenomyosis can be symptomatically identical to endometriosis, but is often diagnosed by transvaginal ultrasound or MRI. Adenomyosis also commonly co-exists with endometriosis.[2] Endometriosis-like symptoms that continue after a normal laparoscopy may be indicative of undiagnosed adenomyosis.

Referral to secondary care for further assessment is recommended if:[9, 10]

- A six-month trial treatment with analgesia and a hormonal medicine is unsuccessful
- The patient has persistent, constant pelvic pain, or significant bowel or bladder pain
- Abnormal findings on pelvic ultrasound
- A pelvic mass is found on examination
- There is a desire for fertility and conception has not occurred following six-months of regular intercourse. N.B. the wait time for a publicly funded appointment for fertility treatment (if eligible) may be up to 12 months.
- Inadequate or no improvement in symptoms following surgical treatment
- The patient has pain or other symptoms that require a significant amount of time off or inability to work or study

Medical management of endometriosis

The aim of medical management is to control symptoms prior to, alongside or instead of surgical interventions. Medical management includes both hormonal and non-hormonal pharmacological treatments; hormonal treatment is based on hormonal suppression of endometriotic lesions and is particularly effective when amenorrhoea occurs via down-regulation of the hypothalamic-pituitary-ovarian axis.[10, 15] However, hormonal treatment may not prevent disease progression, and there are women for whom certain hormonal treatment will not be appropriate, e.g. current or recent history of breast cancer, history of liver tumours.[10]

Endometriosis is a chronic and often relapsing condition and long-term treatment is typically required. Approximately 50% of women will have a recurrence of symptoms within five years if medical management is stopped.[16] Menopause usually leads to a complete cessation of symptoms, even if menopausal hormone therapy is used, although recurrence has been reported in a small number of cases.[17]

For further information on cautions and contraindications to hormonal treatments, see: **https://www.nzf.org.nz/nzf_3892** and **https://www.nzf.org.nz/nzf_4178**

A step-wise treatment strategy

The first-line pharmacological treatment for females with endometriosis who do not wish to conceive in the near future is a hormonal medicine, and analgesics if required.[10]

Progestogen-only treatment (either a progestogen-only oral contraceptive or a progestin) is recommended first-line for suspected or confirmed endometriosis (see below for options).

Combined oestrogen + progestogen treatment (i.e. a combined oral contraceptive [COC]) is an alternative first-line treatment if progestogen-only treatment is not tolerated or suitable (see below for options).[10]

Other hormonal treatment options include gonadotropin-releasing hormone (GnRH) analogues (e.g. goserelin, leuprorelin, buserelin) and androgenic medicines (e.g. danazol), which are used to induce a hypo-oestrogenic state. Adverse effects limit GnRH analogues to a second-line choice that is usually reserved for use in secondary care and androgenic medicines are now rarely used due to their adverse effects.[15] GnRH analogues are associated with several short-term adverse effects, mainly hypo-oestrogenic symptoms, including menopausal symptoms, loss of libido and emotional lability. Long-term adverse effects include bone-mineral density loss. Because of these adverse effects, "add-back" oestrogen-progestogen treatment is recommended if a GnRH analogue is continued for more than six months.[2]

Pain management

A short-course, e.g. three months, of a non-steroidal anti-inflammatory drug (NSAID) or paracetamol, used as required alone or in combination, is recommended for endometriosis-related pain.[9] These can also be used as an adjunct to medical (hormonal) or surgical management options. NSAIDs in particular may be effective at reducing pain and inflammation associated with endometriosis, although evidence from clinical trials is limited and inconclusive.[15, 18] Regular use of opioids is not recommended due to the risks associated with long-term treatment, e.g. dependence, worsening of gastrointestinal symptoms.[10, 19]

If pain is not controlled and a neuropathic component is suspected, a trial of a neuromodulator, e.g. amitriptyline or gabapentin (unapproved indication), may be considered, although there is little evidence of benefit.[20] The adverse effects of these medicines limit their clinical usefulness and short cyclical doses to coincide with menses are not likely to be helpful.

Non-pharmacological treatments to manage pain and other symptoms should be recommended, e.g. a healthy diet, regular exercise and adequate sleep, transcutaneous electrical nerve stimulation (TENS),* pain psychology and referral to specialist women's health physiotherapy.[10]

If pain is unmanaged in primary care despite trialling pharmacological and non-pharmacological interventions, consider seeking advice from a pain clinic.

* Evidence of benefit for women with deep endometriosis has been shown in a small randomised clinical trial[21]

Progestogen-only treatment

High-dose oral progestogens (medroxyprogesterone acetate 30 mg daily or norethisterone 10–20 mg daily[22]) are commonly used to treat endometriosis and have been shown in randomised controlled trials to reduce endometriosis-related pelvic pain.[10] At these doses, progestogens suppress the hypothalamic-pituitary-ovarian axis to inhibit ovulation and reduce circulating oestrogen levels.[10, 16] Progestogens also have an additional, direct effect on the endometrium, causing atrophic change to both normal endometrium and endometriotic lesions.[16]

Progestogens are available in a variety of formulations, including oral medicines, implants, depot injections and intrauterine devices (Table 1). When prescribing progestogens for endometriosis:[10]

- Preferably prescribe at a sufficient dose to produce anovulation and therefore amenorrhoea or oligomenorrhoea
- Consider whether there is a need for contraception when discussing options
- Initiate on the first day of menses
- If troublesome bleeding occurs, try:
  - Increasing the progestogen dose, e.g. doubling it, or changing the formulation
  - Five-day course of oestrogen added to the progestogen treatment (e.g. estradiol valerate [Progynova] 1 mg, once daily)
- If hormone treatment is ineffective after a six-month trial, refer to secondary care

Best practice tip: There is little difference in effectiveness between progestogen formulations, however, patients administered depot progestogen or high-dose oral progestogens may experience more adverse effects. Consider prescribing a progestogen-only oral contraceptive first-line. A trial of a levonorgestrel intrauterine system, i.e. Mirena or Jaydess, is also a reasonable option in some cases, although this may be less effective in women who continue to ovulate.

For further information on POPs, see: **https://bpac.org.nz/2019/contraception/oral-contraceptives.aspx**

For further information on long-acting progestogen-only contraceptives, see: **https://bpac.org.nz/2019/contraception/long-acting.aspx**

Table 1. Progestogen treatments for endometriosis available in New Zealand.[10, 22] N.B. Ongoing supply issues due to COVID-19 are affecting the availability of some medicines; check the PHARMAC website for the latest updates.

Route of administration	Medicine	Dose	Approved for contraception
Oral	Medroxyprogesterone acetate (Provera)	10 mg, three times daily for 90 consecutive days	No
	Norethisterone (Primolut)	5–10 mg, twice daily, for four to six months	No
	Cyproterone acetate [unapproved indication]	50 mg, once daily	No
	Norethisterone (Noriday)*	350 micrograms, once daily	Yes
	Levonorgestrel (Microlut)*	30 micrograms, once daily	Yes
	Desogestrel (Cerazette)*†	75 micrograms, once daily	Yes
Intramuscular injection	Medroxyprogesterone acetate (Depo-Provera)	150 mg, every three months**	Yes
Implant	Levonorgestrel (Jadelle)	2x75 mg rods	Yes
Intrauterine system	Levonorgestrel-IUS 52 mg (Mirena)	Average release of 15 micrograms/day over five years	Yes
	Levonorgestrel-IUS 13.5 mg (Jaydess)	Average release of 6 micrograms/day over three years	Yes

* Variable inhibition of ovulation; desogestrel has a more predictable effect on inhibiting ovulation, however, this formulation is not funded[23]

† Not funded

** The recommended dose for endometriosis is 50 mg weekly or 100 mg every two weeks for at least six months. New Zealand guidance recommends initiating at a lower dose (i.e. 150 mg, three monthly).[10] Consider increasing the dose if bleeding is troublesome or symptoms are uncontrolled. N.B. Depo-Provera is available in 150 mg/mL vials.

Endometriosis and fertility

The pathophysiology of reduced fertility in women with endometriosis is not well understood. Inflammation of the pelvic cavity, structural abnormalities, the presence of endometriomas of the ovaries and possible surgical damage following ovarian endometrioma excision, alterations of sperm-oocyte interaction, reduced endometrial receptivity and co-existing adenomyosis are all thought to be involved.[2]

It is not possible to differentiate between those women with endometriosis who will experience reduced fertility and those who will retain normal levels of fertility, even if a laparoscopy is performed. While caution should be taken when counselling patients, overall reassurance is appropriate for women with possible endometriosis with respect to their future fertility.

Surgery to ablate or excise endometriomas, adhesions and scar tissue is the most common treatment for women with endometriosis who wish to conceive.[9, 27] Flushing of the uterus, fallopian tubes and ovaries with lipiodol (an oil soluble contrast medium) in women with endometriosis has been shown to increase the rate of pregnancy, and may be considered in the setting of a specialist fertility clinic.[32] Assisted fertility treatments are likely to be beneficial for most women with endometriosis who have reduced fertility.[2]

Traditionally, hormonal treatment was used in women with reduced fertility for a short period, e.g. six months, and then stopped, as it was thought that this created "rebound" fertility. However, there is no evidence of benefit; ovulation suppression may delay pregnancy and is not recommended.[27]

Pregnancy is often considered as beneficial for women with endometriosis in terms of symptom management and disease progression. However, the limited evidence available suggests that this is not universal; some lesions may regress during pregnancy, while others may remain stable or even increase.[33] Pregnancy-associated amenorrhoea likely decreases the risk of new lesions forming.[33] Some women may experience complete resolution of endometriosis-associated pain, while others may have an increase, e.g. from endometrial lesions growing on the bladder, rectum or umbilicus.[33] Pregnancy may reduce the risk of endometriosis recurrence, although the data are limited and interpretation is complicated by the fact that endometriosis stage at diagnosis influences the likelihood of pregnancy.[33]

Combined oral contraceptives

Combined oral contraceptives (COCs) are widely used to treat women with suspected endometriosis and are often used first-line, although they have not been approved for this indication and there is limited evidence of benefit.[10, 15] COCs prevent ovulation and endometrial proliferation.

The choice of COC should be based on any previous use by the patient. A reasonable option for a first-time COC user is 30–35 micrograms ethinylestradiol with either 150 micrograms levonorgestrel or 500 micrograms norethisterone. A lower dose of ethinylestradiol (≤ 30 micrograms) is recommended for women aged > 40 years.[24]

COCs should be used continuously or semi-continuously, e.g. three or six-month cycles, as monthly uterine bleeds are still likely to be painful, although less so than normal menstruation when not taking a COC.[25] Patients should be advised that this may result in irregular spotting and occasional breakthrough bleeding.

N.B. Ongoing supply issues due to COVID-19 are affecting the availability of some COCs; check the PHARMAC website for the latest updates (**https://pharmac.govt.nz/medicine-funding-and-supply/medicine-notices/oral-contraceptives/**).

For further information on COCs, including cautions and contraindications to treatment, see: **https://bpac.org.nz/2019/contraception/oral-contraceptives.aspx**

Surgical treatment

Surgical treatment can be effective for reducing pain and other symptoms, and may increase fertility in women with reduced fertility.[2] However, even when performed, recurrence rates of endometriosis can be high and further surgery required: 20–40% of women re-develop symptoms within five years of surgery, although rates vary by subtype.[26] Hormonal treatment, e.g. levonorgestrel-IUS, following surgery can reduce the risk of recurrence and need for further surgery.[27]

The success rate of surgical treatment of endometriosis depends on the severity of the condition, its location, and the type of the symptoms as well as the age of the patient (effectiveness is higher in older women, which is thought to be due to the natural decline in oestrogen production).[28]

Surgery for endometriosis is divided into two strategies:

Conservative surgery (or surgery with preservation of fertility) involves laparoscopy to ideally excise all visible lesions and restore pelvic anatomy. It is the more common surgical option, which significantly reduces pain in the majority of patients and has the ability to retain, and in some cases improve, fertility.[2] The rate of symptom recurrence is higher than with more aggressive, non-preservative techniques, however, the ability to maintain fertility outweighs this for many women.[2]

Radical surgery is limited to women with endometriosis who do not wish to conceive, and after all medical treatments have been unsuccessfully trialled. Often, conservative surgery will also have been undertaken previously. More aggressive surgical options include hysterectomy, bilateral salpingectomy (removal of the fallopian tubes) and bilateral oophorectomy (removal of the ovaries). The excision of all visible peritoneal lesions is the gold-standard in addition to hysterectomy. Patients undergoing radical surgery should be counselled about the possibility of symptoms persisting even after complete bilateral oophorectomy and hysterectomy, and the adverse effects associated with early, medically-induced menopause. Menopausal hormone therapy can be used to manage menopausal symptoms.[27] In general, conservation of normal ovaries is preferred. Endometriosis is associated with a small increase in the risk of ovarian cancer; bilateral salpingectomy can be offered to those who do not wish to conceive to reduce this risk by 30–60%.[29, 30]

For further information on menopausal hormone therapy, see: **https://bpac.org.nz/2019/mht.aspx**

Complications of endometriosis surgery

Common complications associated with endometriosis surgery include adhesion formation and decreased ovarian reserve post-surgery.

Adhesions are thought to result from the inflammation of peritoneal surfaces, which may be increased by surgical intervention. Sequelae may include pain, structural changes to the pelvic and reproductive organs and much less commonly bowel obstruction.

Ablation of ovarian endometriomas is associated with decreased ovarian reserve, particularly in patients with bilateral cysts, and great care must be taken when using diathermy.[2] Even with conservative surgical interventions, 2.4% of women develop primary ovarian insufficiency (also known as primary/premature ovarian failure).[31]

Deep infiltrating endometriosis surgery can be associated with major complications including bowel injury, ureteric injury, post-operative infection, rectovaginal fistula, neurogenic bladder and bowel dysfunction.[2]

Final thoughts

Ensuring that women with suspected endometriosis feel validated is one of the most important roles of primary care. Often patients will have endured endometriosis symptoms for many years, perhaps even considering them to be "normal" or feeling dismissed if they did seek help. Acknowledging the impact endometriosis has on the patient's quality of life and providing psychological support, including referral if necessary, should be a focus of primary care clinicians, while management strategies are explored.

Information and support for patients is available from Endometriosis New Zealand: **https://nzendo.org.nz/**

For further information on the diagnosis and management of endometriosis, see: **www.health.govt.nz/system/files/documents/publications/diagnosis-and-management-of-endometriosis-in-new-zealand-mar2020_0.pdf**

An eLearning module on endometriosis, covering symptoms, management and 'whole-person' care, is available from the Royal Australian and New Zealand College of Obstetricians and Gynaecologists: **https://www.climate.edu.au/mod/page/view.php?id=13314**

Patient information on endometriosis treatment options is available from:

- Health Navigator: **www.healthnavigator.org.nz/health-a-z/e/endometriosis-treatment/**
- The Royal Women's Hospital Australia: **www.thewomens.org.au/health-information/periods/endometriosis/treating-endometriosis**
- National Institute for Health and Care Excellence: **www.nice.org.uk/guidance/ng73/resources/patient-decision-aid-hormone-treatment-for-endometriosis-symptoms-what-are-my-options-pdf-4595573197**

Summary on managing suspected endometriosis in primary care:

1. Obtain a clinical history and exclude differential diagnosis as far as possible.
2. Perform an abdominal examination and, if appropriate, undertake a bimanual vaginal examination. If an abnormality is found on examination, request a pelvic ultrasound and refer to a gynaecologist.
3. If endometriosis is suspected, initiate NSAIDs (taken as required) and a hormonal medicine (e.g. POP or COC); consider other progestogens, but titrate the dose to avoid adverse effects. Refer women who wish to conceive to a gynaecologist.
4. Ideally, every patient with suspected endometriosis should have a pelvic ultrasound, including a transvaginal scan if they consent.
5. Refer to gynaecology if no significant improvement within six months, or sooner if the woman has significant anxiety and local referral pathway allows.

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N.B. Expert reviewers do not write the articles and are not responsible for the final content. bpac^{nz} retains editorial oversight of all content.

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Withdrawing patients from long-term use of benzodiazepines or zopiclone

Stopping benzodiazepine or zopiclone treatment in people who have been taking these medicines long-term can be challenging. Strategies to encourage patients to stop a benzodiazepine or zopiclone should involve education to realign their perceptions of risks and benefits, non-pharmacological approaches to manage insomnia or anxiety, and gradual tapering of the dose.

Easy to start, hard to stop

Most general practitioners in New Zealand are likely to have patients in their practice who have been taking benzodiazepines or benzodiazepine-like hypnotics long-term. These patients may have initially been prescribed these medicines by another doctor or at another practice many years ago, which has then been continued due to perceived benefit or difficulty withdrawing. While these medicines can provide effective short-term symptom relief, e.g. of anxiety or insomnia, there are other non-pharmacological and pharmacological strategies that are more appropriate and effective long-term. Each time a patient presents for a repeat prescription is an opportunity for review and a discussion about possible discontinuation.

Take a "slow but sure" approach

Rapid withdrawal of benzodiazepines in people who have been taking these medicines regularly is associated with an increased risk of seizures, therefore patients should be counselled against stopping their medicine abruptly.

Acute withdrawal can result in physiological and psychological effects, and a dose reduction strategy that aims to slowly wean patients off benzodiazepines and zopiclone is best practice. A gradual taper has been shown to improve the rate of successful discontinuation and avoid effects of withdrawal.[1] There is little evidence, however, of how frequently doses should be reduced, by how much, or over what time frame; this is individually variable. Educational strategies to help realign the patient's perceptions about the risks and benefits of treatment should be included in any withdrawal plan.[2, 3]

General recommendations for benzodiazepine or zopiclone withdrawal[1]

Individualise the withdrawal schedule based on the indication, dose, duration and type of medicine (e.g. short-acting vs. long-acting) as the response can be variable between patients.

Reduce the dose slowly to the lowest available dose formulation followed by planned medicine-free days (see below for an example of a de-prescribing algorithm or refer to the NZF: **https://www.nzf.org.nz/nzf_1991**).

Increasing the dispensing frequency, e.g. to weekly,* set days of the week or daily is a useful strategy; more frequent dispensing helps patients adhere to the withdrawal plan and reduces the risk of taking doses early and running out, which in turn can lead to withdrawal symptoms or pressure for another prescription or picking up repeat prescriptions early. More frequent contact with the pharmacist can also increase the amount of support the patient is receiving and helps to reduce anxiety about the withdrawal plan. N.B. This approach will not be appropriate for all patients, e.g. if a pharmacy is not easily accessible.

* Benzodiazepines are Class C controlled drugs. All controlled drugs are automatically dispensed once every ten days; by specifying "weekly" dispensing on the prescription the pharmacist can more easily identify when patients are collecting prescriptions early than with a ten-day cycle (because the day of the week changes).

Transition patients who are taking a short-acting benzodiazepine to diazepam as it is less likely to cause withdrawal symptoms when tapered due to its long half-life. The New Zealand Formulary contains dose equivalence data to assist in switching benzodiazepines, as well as guidance for benzodiazepine withdrawal: **https://nzf.org.nz/nzf_2001**

Remind patients who are using benzodiazepines or zopiclone for insomnia to only take the medicine if they are unable to fall asleep on their own, e.g. after two hours, rather than taking the medicine routinely at bedtime.

Provide written documentation of the treatment plan so that both patient and clinician can keep track of the planned reduction strategy. This is especially useful for patients who may be experiencing memory loss associated with treatment.

Provide the patient with information about discontinuing benzodiazepines, e.g.:

- "Stopping benzodiazepines and Z-drugs" available from: **http://medical.cdn.patient.co.uk/pdf/4638.pdf**
- "Step by step guide: reducing from benzodiazepines and recovery from withdrawal " available from: **http://www.reconnexion.org.au/resources**

Monitor progress with regular contact, e.g. phone calls from the practice nurse.

Be flexible – adjust reduction intervals according to how well a patient is tolerating the process. Some patients may manage a relatively quick reduction while others require a longer withdrawal process, e.g. this may take one month for every year of use.

If patients are experiencing difficulty, encourage them to remain on the lower dose they have achieved at that point, rather than increase the dose again. Recommence dose reduction when the patient feels able to resume.

Discuss the possibility of withdrawal symptoms, e.g. tremor, irritability, insomnia and anxiety; reassure patients that these symptoms are temporary and should alleviate once the withdrawal process is complete.

For patients with ongoing symptoms of anxiety or depression, the use of antidepressants in addition to psychological support may be required.

N.B. counselling or referral to psychological support services substantially improves rates of discontinuation over and above patient education or follow-up approaches, however, access to these services may be limited.

Resources for clinicians:

An example of a "de-prescribing" algorithm for benzodiazepines and zopiclone is available from: **https://deprescribing.org/wp-content/uploads/2019/02/BZRA-deprescribing-algorithms-2019-English.pdf**

Further information for clinicians on managing benzodiazepine dependence is available from: **https://www.nps.org.au/news/managing-benzodiazepine-dependence-in-primary-care**

For general information on benzodiazepines and zopiclone, see: **https://bpac.org.nz/bpj/2015/february/benzodiazepines.aspx**

Consider discussion with an addiction specialist or referral to addiction services

For patients who have difficulty withdrawing from benzodiazepines or zopiclone, such as those who find the process psychologically distressing or who develop strong withdrawal symptoms, consider discussing their situation with an addiction specialist or referring to addiction services; these patients may need more in-depth assistance than can be easily offered in a general practice setting.

Patients who have been taking benzodiazepines or zopiclone at high doses (e.g. > 20 mg diazepam per day) or for a long period of time (e.g. > ten years) are best discussed with an addiction specialist if they are withdrawing from treatment. These patients are likely to require a lengthy withdrawal period and more intensive psychological support and counselling.

N.B. Be aware that some patients may not actually be taking the benzodiazepines or zopiclone prescribed to them; anecdotally, drug-seeking rings commonly include older women who may raise less suspicion than younger males.

Patient support for benzodiazepine and hypnotic withdrawal

Some patients may find benefit from interacting with others in a similar situation, or those who have prior experience with hypnotic addiction. This may be in the form of face-to-face patient-focused support groups (if available locally) or online support (see links below). Other support within the healthcare system or wider community, e.g. counselling, is also available for patients with addiction to medicines, however, access may be limited.

New Zealand drug and addiction resources and services:

- Drug Help: **www.drughelp.org.nz**
- Addictions treatment directory: **www.addictionshelp.org.nz/Services/Home**
- New Zealand Drug Foundation: **www.drugfoundation.org.nz**
- Alcohol drug help line: **0800 787 797**
- Salvation Army addiction support: **0800 530 000**
- Narcotics Anonymous: **www.nzna.org**

Online information and support groups:

- **www.benzobuddies.org**
- **www.benzosupport.org**

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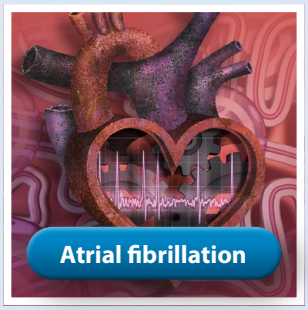

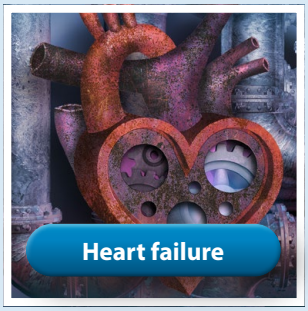

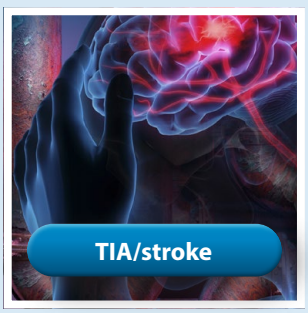

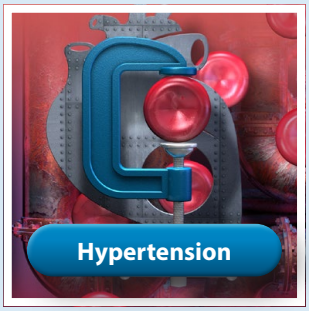

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