CHRONIC DISEASE MANAGEMENT 2022
https://doi.org/10.33591/sfp.48.1.uo1

INFLAMMATORY BOWEL DISEASE – AN UPDATE FOR PRIMARY CARE PHYSICIANS

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ABSTRACT

Inflammatory bowel disease (IBD) is a chronic, idiopathic, inflammatory disorder of the gastrointestinal tract that is typically categorised into Crohn's disease and ulcerative colitis. Traditionally, IBD was regarded as a disease of the western world. Newer epidemiological studies suggest that, with the turn of the 21st century, IBD has become a global disease with rising incidence in newly industrialised countries in Asia, Africa, and South America. There are also advances in the diagnostics and therapeutic armamentarium of IBD. In this review, we provide an update on the epidemiology, clinical features, investigations, and management of IBD. We also highlight the importance of vaccination in IBD and provide practical points for family physicians.

Keywords: Inflammatory Bowel Disease, Epidemiology, Clinical features, treatment, vaccination

SFP2022; 48(1): 49-58

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic, idiopathic, inflammatory disorder of the gastrointestinal tract that is typically categorised as one of two subtypes: Crohn's disease (CD) and ulcerative colitis (UC).[1] It is characterised by episodes of relapse and periods of remission. CD can affect any segment of the gastrointestinal tract from the mouth to the anus and is characterised by transmural inflammation that can lead to various complications such as strictures, fistulas, and abscesses. UC, in contrast, is limited to the colon, with mucosal inflammation that extends proximally in a continuous manner, and can lead to erosions, ulcers, severe bleeding, toxic megacolon, and fulminant colitis. The pathogenesis of IBD remains elusive, but involves complex interplay between genetic, environmental, epithelial, microbial, and immune factors.[2]

Traditionally, IBD was considered to be a disease of the western world and rare in resource-limited countries in Asia, Africa, and South America. The western world can be defined as consisting of countries influenced by a western European cultural heritage, and includes the USA, Canada, Australia, New Zealand, and all countries in western Europe.[3] New evidence has elucidated the changing global epidemiological trends of IBD. The therapeutic armamentarium in IBD has also expanded over the past two decades and comprises untargeted therapies, such as 5-aminosalicylates (5-ASA), glucocorticoids, and immunomodulators, as well as targeted biological agents and small molecules.

In this article, we review the epidemiology, clinical features, investigations, and management of IBD. We also highlight the importance of vaccination in IBD and provide practical points for family physicians.

EPIDEMIOLOGY

The incidence of IBD has increased sharply in the western world since UC and CD were first described in 1859 and 1932 respectively. The incidence and prevalence of IBD differs greatly by geographic region, with the highest incidence of both CD and UC reported in North America, Europe, and Oceania. The annual incidence of CD ranged from 6.3 to 23.8 per 100,000 person-years in North America, 0 to 15.4 per 100,000 person-years in Europe, and 13 to 29.3 per 100,000 person-years in Oceania from 1990 to 2016.[3] Similar to CD, the annual incidence of UC ranged from 8.8 to 23.1 per 100,000 person-years in North America, 0.6 to 24.3 per 100,000 person-years in Europe, and 7.3 to 17.4 in Oceania from 1990 to 2016 (Figures 1 and 2).[3] Between 1990 and 2017, the number of prevalent IBD cases increased from 3.7 million (95 percent uncertainty interval (UI) 3.5-3.9) to more than 6.8 million (6.4-7.3).[4]

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Figure 1

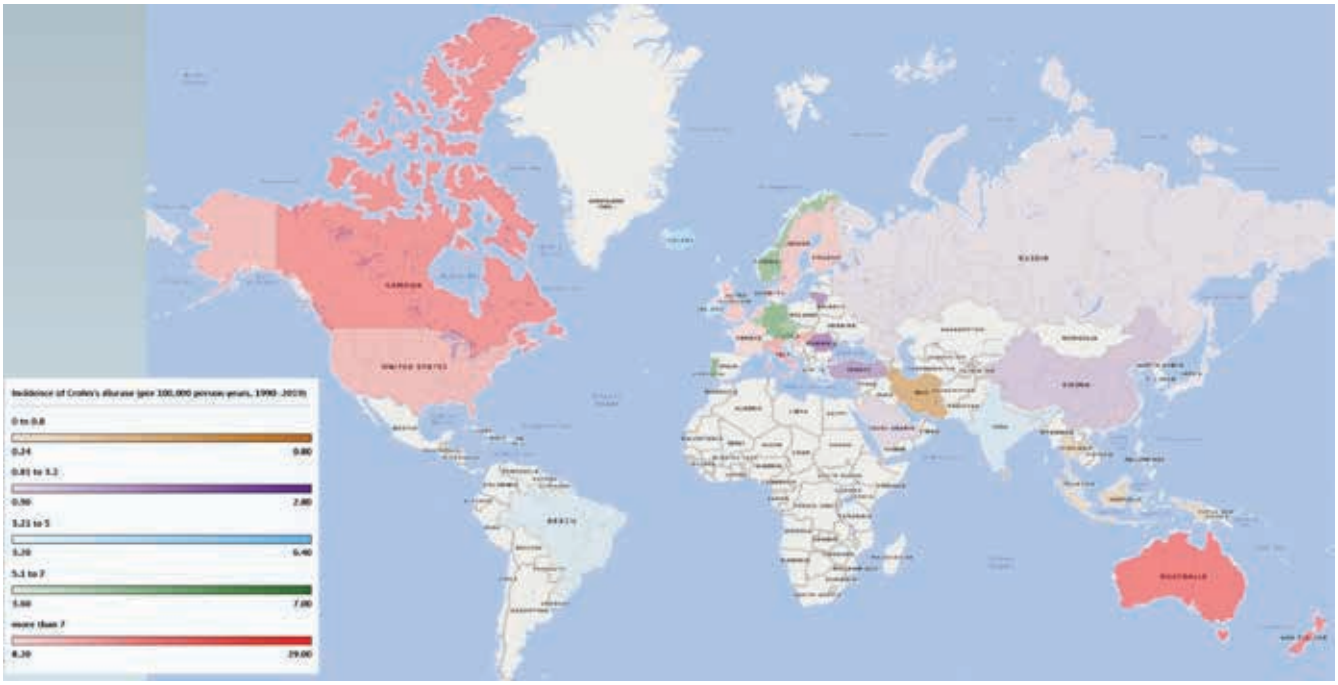
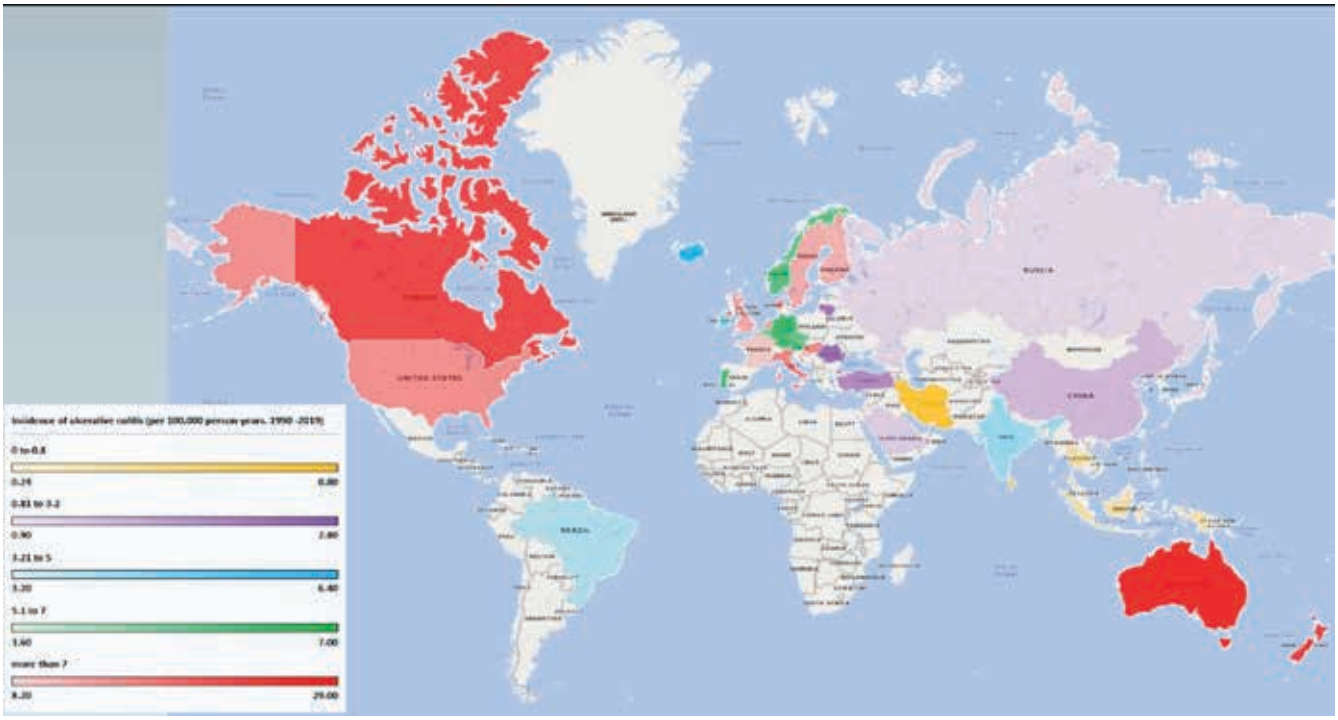


Figure 2



Newer epidemiological studies suggest that, with the turn of the 21st century, IBD has become a global disease with rising incidence in newly industrialised countries in Asia, Africa, and South America, that have transitioned to a more westernised society, whereas the incidence is stabilising in the west.[3] The incidence and prevalence of IBD in India are highest among Asian countries, although they are much lower than those in Western countries.[5] The Asia-Pacific Crohn's and Colitis Epidemiology Study (ACCESS) reported the annual incidence of IBD, UC, and CD in India between 2012 and 2013 at 9.31, 5.40, and 3.91 per 100,000 respectively.[5] The corresponding annual incidence of IBD, UC, and CD in Singapore during the same period of study were 1.14, 0.44, and 0.70, respectively.[5] The prevalence of IBD in Asian populations has also increased.

CLINICAL FEATURES OF INFLAMMATORY BOWEL DISEASE

Ulcerative Colitis

Ulcerative colitis is a chronic, inflammatory disease that affects the colon, and most commonly presents in adults between 20 and 50 years of age. Typical symptoms in UC include increased frequency of bowel movements, blood and/or mucus in the stool, tenesmus or urgency, nocturnal defecations, and abdominal discomfort. Up to 15 percent of patients may initially present with acute severe ulcerative colitis (ASUC).[6] ASUC is a potentially life-threatening condition, characterised by clinical and laboratory features using the modified Truelove and Witts criteria.[6] Ulcerative colitis is classified by the extent of colonic involvement, namely proctitis, left-sided colitis, and extensive colitis. Clinical presentation might vary depending on the disease extent. For example, patients with proctitis might predominantly have urgency and tenesmus (sensation of incomplete evacuation), whereas in pancolitis, bloody diarrhoea and abdominal pain might be more obvious. Up to 10 percent of patients with proctitis or left-sided colitis can suffer from paradoxical constipation.[7]

Crohn's Disease

Unlike Ulcerative Colitis, which only affects the colon, Crohn's Disease can involve any segment of gastrointestinal (GI) tract, from the mouth to the anus.[8] Hence, the presentation for CD is more variable and is dependent on the severity, phenotype, and location of the disease. The location of inflammation in CD is relatively stable, but changes in disease behaviour can occur throughout the disease course.[9,10] Whereas the most common initial presentation of CD is uncomplicated inflammatory disease, more than 70 percent of CD patients develop a stricturing or penetrating complication within 10 years of diagnosis.[9,10] Signs and symptoms of CD include abdominal pain, watery diarrhoea, weight loss, and fatigue. The abdominal pain occurs frequently at the right lower quadrant in view of CD's predilection for involving terminal ileum and often persists for many years before diagnosis is made. Fibrostenosing Crohn's disease, defined as persistent luminal narrowing,[11] affects more than one-third of CD patients and results from intestinal fibrosis.[12] Patients could present with obstructive symptoms such as abdominal pain and vomiting. Stricturing and penetrating disease commonly co-exist in the same patient. Fistulae, which are abnormal communications between two or more epithelialised surfaces, can be a manifestation of penetrating Crohn's disease.[13] They can be classified into external and internal fistulae. External fistulae have a communication to the skin and include enterocutaneous and perianal fistulae. Internal fistulae have connection between the bowel and any internal orangs such as the bowel (enteroenteric), bladder (enterovesical), and vagina (enterovaginal). The pathophysiology of fistulae in CD is poorly understood but factors involved in the pathogenesis include a genetically determined aberrant immune response with increased production of cytokines, resulting in upregulation of matrix metalloproteinases and epithelial-to-mesenchymal transition.[14] While enteroenteric fistula is usually asymptomatic, passage of stool or gas through the vagina or bladder can occur in enterovaginal fistula and enterovesical fistula respectively.[8] Up to one-third of CD patients may present with perianal disease such as fistula, fissure, abscesses, and skin tag. The development of perianal fistula is thought to represent a more aggressive form of the disease, which requires a combination of medical and surgical therapy.[15]

EXTRAINTESTINAL MANIFESTATIONS

Up to 50 percent of patients with IBD may experience at least one extraintestinal manifestation (EIM), which may adversely impact upon patients' quality of life.[16] EIMs are more common in CD than UC, particularly in patients with colonic CD, with the exception of primary sclerosing cholangitis, which usually affects UC more than CD.[16] EIMs can affect multiple body systems, including ocular, oral, dermatological, musculoskeletal, and hepatobiliary systems. Most EIMs run in parallel with intestinal disease activity with the exception of ankylosing spondylitis and uveitis.[16] The management of EIMs usually involves a multidisciplinary team of IBD physician, rheumatologist, dermatologist, and ophthalmologist.

INVESTIGATIONS

The diagnosis of IBD requires a combination of clinical, biochemical, stool, endoscopic, cross-sectional imaging, and histological investigations.[17-21]

Biochemical – Blood

Although the diagnosis of IBD cannot be made through a simple blood test, initial laboratory investigations should include full blood count, renal panel, serum albumin, and

C-Reactive Protein (CRP). These blood investigations would aid in evaluation for inflammation, anaemia, dehydration, and malnutrition.[17-19]

Routine use of serologic markers for the diagnosis of IBD is not recommended.[17,18] Autoantibodies such as *perinuclear antineutrophil cytoplasmic antibodies* (pANCAs) and *anti-saccharomyces cerevisiae antibodies* (ASCAs) have been associated with diagnosis of UC and CD respectively. However, the sensitivity of such tests is low, making their use for the diagnosis of IBD less helpful.[17,18] There is some utility of using these tests to differentiate between CD and UC though it is not routinely performed.[17,18]

Biochemical – Stool

Faecal calprotectin measurement is a study of which calprotectin, a calcium-containing antimicrobial protein complex, is evaluated from stool sample. This protein complex makes up 60 percent of the cytosolic protein in neutrophils, which is released during acute and chronic inflammation of the GI tract wall.[20] Faecal calprotectin is a useful investigation to distinguish IBD from irritable bowel syndrome (IBS).[20] As faecal calprotectin levels correlate significantly with clinical or endoscopic disease activity in IBD, they can be used to guide therapeutic decisions. Of note, faecal calprotectin level can be elevated in other causes of intestinal pathologies such as colorectal neoplasia, drug-induced enteropathy (such as non-steroidal anti-inflammatory drugs), infectious gastroenteritis and diverticulitis.[20] Thus, the use of faecal calprotectin needs to be correlated with the appropriate clinical condition prior to interpretation of the value.[19]

Endoscopy and Histology

Ileocolonoscopy with intubation of the terminal ileum and biopsy is recommended as part of the initial evaluation of patients with suspected IBD, while upper endoscopy is only performed in adult patients with upper gastrointestinal signs and symptoms.[17-19] The endoscopic hallmark of CD includes a patchy distribution of inflammation and skip lesions. Other lesions found in CD are aphthous erosions (with diameter <5 mm) and ulcers (with diameter >5 mm) that tend to be longitudinal with a cobble-stone appearance.[8] On the other hand, UC most often presents endoscopically as a continuously inflamed segment involving the rectum and extending proximally. The endoscopic features include loss of vascular markings, friability of the mucosa, erosions, granularity, and deep ulcerations and spontaneous bleeding when inflammation is severe. There is often a line of demarcation at the proximal extent of disease with an abrupt transition to normal mucosa.[21]

In patients suspected to have IBD, it is pertinent to perform a histologic examination before commencement of treatment. A minimum of two biopsies from at least five sites along the colon, including the rectum and the terminal ileum, should be obtained.[22] The features that most strongly support a diagnosis of IBD in a biopsy are basal plasmacytosis and architectural changes. Histological distinction between UC and CD in clinical practice may be difficult. The histological diagnosis of UC is based on the combination of diffuse crypt architectural distortion and mucosal atrophy, and a diffuse transmucosal inflammatory infiltrate with basal plasmacytosis, with cryptitis and crypt abscesses.[22] Diagnostic features of CD are a discontinuous or focal chronic inflammation with focal crypt irregularity and granulomas.[22]

Imaging

Currently, small bowel capsule endoscopy is reserved for patients with high suspicion of CD after a negative ileocolonoscopy and radiological findings. If capsule endoscopy shows possible lesions in small bowels, a device-assisted enteroscopy may be needed to obtain biopsies for histological diagnosis.[19]

Small bowel imaging, such as computerised tomography enterography (CTE), magnetic resonance enterography (MRE), and bowel ultrasonography (BUS), should be performed as part of the initial diagnostic workup for patients with suspected CD to assess the disease extent and to detect inflammatory complications (for instance, strictures, fistulas and abscesses) along the GI tract.[18,19] Bowel ultrasonography has emerged as an inexpensive, non-invasive, and radiation-free tool for accurate assessment of the intestinal wall and extraluminal manifestation.[18,19] All three modalities have comparable (and high) accuracy.

MANAGEMENT

The goal of IBD management is to preserve the patient's quality of life and to reduce the rates of developing complications from uncontrolled inflammation. Early decisive intervention results in effective symptom control, bowel healing, and ultimately prevention of bowel damage and disability.[23] Symptom resolution alone is not an acceptable end point in IBD management as newer targets of treatment such as improvement in biochemical markers, mucosal healing, and normalisation of quality of life have been established.[24]

Clinical remission entails an absence of diarrhoea, rectal bleeding, and abnormal pain. Biochemical remission is achieved with normal C-reactive protein and stool calprotectin levels. Mucosal healing is defined as the absence of ulcers on endoscopy. Histological remission is defined by the lack of active inflammation on histology. An effective treatment would meet these targets at different periods. Realistically, clinical remission should be achieved in weeks to months, whereas histological remission would often take a longer time, up to a year.[24]

A treat-to-target strategy is adopted with scheduled assessments to determine if treatment targets are met along the course of disease. When treatment is deemed to be suboptimal, adjustments such as escalation in medication doses or switching therapies will need to be considered.

Broadly speaking, there are two phases in treatment: inducing and maintaining remission. Steroids are useful in both UC and CD but have unfavourable side effects profile and thus are useful only in inducing remission. 5-ASA compounds are used for both induction and maintenance in mild-moderate UC but not in CD. The slow onset of action of immunomodulators limits their use to maintenance therapy. Azathioprine can be used in both UC and CD but methotrexate is effective only for CD. Biologics are monoclonal antibodies targeted against cytokines or cell receptors. Anti-TNFs (infliximab, adalimumab), anti-integrin (vedolizumab), and anti-IL12/23 (ustekinumab) have been proven to work in IBD patients with moderate-severe disease. In general, vedolizumab and ustekinumab have a better safety profile due to more selective targeting; however, anti-TNFs have been proven to be durably effective with many years of clinical experience.[17-19] Small molecules are the newest class of agents, with a JAK inhibitor (tofacitinib) being licensed for use in Singapore for UC. The development of selective JAK inhibitors is in progress and will be available in the coming years.[25]

Factors that predict a disabling disease course would warrant initial aggressive therapy with biologics. These factors include young age of onset, high disease activity at presentation, extensive bowel involvement, use of steroids, and fistulising phenotype.[26] The rationale behind this strategy is that early amelioration of inflammation would limit the extent of bowel damage and fibrosis. Once fibrosis has been firmly established, treatment with anti-inflammatory agents is unlikely to reverse the disease course.

Treatment options should be discussed with patients, as these are medium- to long-term therapies with variable efficacies and possible side effects, which include serious infections and malignancies. Patients' preferences are important as acceptability affects compliance to assessments and treatment. Shared decision making is fundamental to a strong patient-physician relationship.[27]

VACCINATION IN IBD

Patients with IBD are at increased risk of infections, both from the disease state itself[28] and the effect of immunosuppressive treatment.[29,30] Notably, many of these infections could be prevented by vaccinations.[31-35] Furthermore, vaccine-preventable diseases in IBD are associated with higher rate of hospitalizations,[33-35] longer hospitalisations,[35] higher hospitalisations costs,[35] and mortality.[34-36]

While several international guidelines have been published,[37,38] vaccination rates in patients with IBD remain suboptimal and lower than those in the general population. In a recent systematic review,[39] the median rates of vaccination against influenza, pneumococcal pneumonia, hepatitis B, and herpes zoster were reported at 42 percent, 20 percent, 48 percent, and 11 percent, respectively.[39] The low vaccination rate could be related to patient and physician factors. The reasons for vaccine hesitancy among IBD patients, defined as a delay in acceptance or refusal of vaccination despite availability of vaccination services,[40] include concern about vaccine side effects,[41] lack of awareness about the importance and safety of vaccines in immunocompromised patients,[41] and misconceptions about vaccination.[41,42] The reasons of vaccine hesitancy among physicians include lack of concern for vaccinations, insufficient consultation time, and knowledge gaps regarding vaccinations.[43-45] One additional reason of vaccine hesitancy among physicians seems to be the lack of clarity as to which physician (gastroenterologist or primary care physician) is responsible for recommending and providing age-appropriate vaccines.[46] In a survey of family care physicians,[47] although two-thirds of the gastroenterologists thought that the primary care physician was responsible for determining which vaccinations to administer to the IBD patient, only 30 percent of family medicine practitioners were comfortable making a recommendation for vaccinating their IBD patients. The Infectious Diseases Society of America (IDSA) guideline[48] recommends that specialists who care for immunocompromised patients share responsibility with the primary care provider for ensuring that appropriate vaccinations are administered to immunocompromised patients. The treating gastroenterologist could make vaccination recommendations to the patients, but the actual administration of these vaccines may be a shared responsibility.[38,48] Hence, concise communication on specific vaccine recommendations to the primary care team is crucial.

The two main types of vaccinations comprise inactivated vaccines and live attenuated vaccines. With reference to current guidelines,[19,38,48,49] the ideal time to vaccinate IBD patients is at the time of diagnosis of IBD. All adult patients with IBD, regardless of immunosuppression status, should receive inactivated vaccines in accordance with national guidelines,[19,38,48-50] such as inactivated influenza vaccine (trivalent/quadrivalent), pneumococcal vaccine (PCV13 and PPSV23), hepatitis A vaccine, hepatitis B vaccine, recombinant zoster virus vaccine, and human papilloma virus (HPV) vaccine. In general, inactivated vaccines should be administered ≥2 weeks before immunosuppression. For patients receiving immunosuppressive treatment, live vaccines are generally contraindicated and their use can be considered only at least four weeks before or three months after discontinuing immunosuppressive therapy. [19,38,48,49] A list of vaccines recommended in patients with IBD is listed in Table 1.

Table 1. IBD-specific vaccination programme[12,31,41-43]

Vaccines	Type of vaccine	Strongly recommended before immunosuppressive treatment	Dosing regimen
Influenza	Non-live	Yes	• Annual immunisation with trivalent/ quadrivalent inactivated influenza vaccine. • Live attenuated intranasal influenza vaccine is contraindicated in immunosuppressed patients
Pneumococcal conjugate 13-valent [PCV13] and polysaccharide [PPSV23]	Non-live	No	• Single dose of PCV13 followed by PPSV23 after 8 weeks, and a PPSV23 booster after 5 years. Additional PPSV23 booster according to national guidelines. • If PPSV23 provided first, then administer a single dose of PCV13 after 1 year and a PPSV23 booster after 5 years. Additional PPSV23 booster according to national guidelines
Hepatitis A	Non-live	-	2 doses at 0 and 6 months
Hepatitis B	Non-live	Yes	3 doses at 0, 1–2 and 4–6 months
HPV	Non-live	-	Two or three doses depending on age, for unvaccinated patients, both sexes
Recombinant zoster vaccine	Non-live	Yes	• Preferred over live zoster vaccine. • For all patients ≥50 years. • Consider in patients <50 years at increased risk of herpes zoster infection
Live zoster vaccine	Live-attenuated vaccine	Yes	Use only if recombinant zoster vaccine is unavailable and patient is immunocompetent

CONCLUSION

In summary, inflammatory bowel disease is a chronic, progressive, immune-mediated disease that has an increasing global incidence. Early diagnosis and prompt institution of treatment are key to improve outcomes and reduce complications. The armamentarium of IBD medications has expanded over the years, and risk stratification of disease severity could guide selection of first-line therapy. Lastly, patients with IBD are at increased risk of infections, many of which could be prevented by vaccinations. It is therefore important for physicians to recommend appropriate vaccinations for prevention of infectious diseases in patients with IBD.

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LEARNING POINTS

- **Recent evidence suggests that at the turn of the 21st century, IBD has become a global disease, with rising incidence in newly industrialised countries such as Asia, Africa, and South America.**
- **The diagnosis of IBD requires a combination of clinical, biochemical, stool, endoscopic, cross-sectional imaging, and histological investigations.**
- **In addition to conventional therapies such as aminosalicylates, glucocorticoids, and immunomodulators, the therapeutic armamentarium of IBD has expanded and includes anti-TNFs (infliximab, adalimumab, certolizumab and golimumab), anti-integrin (vedolizumab), and anti-IL12/23 (ustekinumab), as well as JAK inhibitor (such as tofacitinib).**
- **Patients with IBD are at increased risk of infections. It is therefore important for physicians to recommend appropriate vaccinations for prevention of infectious diseases in patients with IBD.**