

WGO Handbook on
**Inflammatory
Bowel Disease (IBD):
Navigating Evolving
Therapies In An
Evolving Disease**

**WORLD DIGESTIVE
HEALTH DAY
MAY 29, 2017**



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Inflammatory Bowel Disease

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World Digestive Health Day

WDHD – May 29, 2017

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Message from the Chair, World Digestive Health Day 2017 Inflammatory Bowel Disease (IBD): Navigating Evolving Therapies in an Evolving Disease

Dear Colleagues,

Inflammatory bowel disease (IBD) is a group of idiopathic chronic inflammatory intestinal conditions. The two main disease categories are Crohn's disease (CD) and ulcerative colitis (UC), which have both overlapping and distinct clinical and pathological features.

The pathogenesis of IBD is incompletely understood. Genetic and environmental factors such as altered luminal bacteria and enhanced intestinal permeability play a role in the dysregulation of intestinal immunity, leading to gastrointestinal injury. In the absence of knowing definite causes of IBD there are currently several therapies that dampen the aberrant immune response. Some therapies in development are aimed at the gut microbiome. These therapies can range from diet supplements to fecal transplantation. As IBD is increasingly a worldwide disease one challenge will be to determine if therapies proven to be effective in one population will be comparably effective in another. Another challenge will be to facilitate access to novel expensive therapies in lesser privileged countries.

The World Gastroenterology Organisation (WGO) has raised awareness of IBD through its annual public advocacy and awareness campaign, World Digestive Health Day (WDHD). WDHD is celebrated each year on May 29th with associated activities and initiatives continuing throughout and beyond the campaign year. WDHD will provide gastroenterologists, their patients and the lay public, with an understanding of the latest basic and clinical research in the pathogenesis, investigation and treatment of IBD. This campaign seeks to translate research into clinical practice and facilitate communication between physicians, pharmacists, allied health professionals, healthcare payers and the public. We want to ensure that patients receive appropriate dietary and lifestyle advice as well as appropriate investigations and treatment, relevant to their condition and circumstances. We want to ensure awareness of the disease and its management is raised in countries where IBD is being increasingly and newly diagnosed.

The WGO's task will be supported by a Steering Committee with a global perspective. The Steering Committee will provide expertise on IBD, guiding the course of the campaign and the development of the educational and training materials, in collaboration with WGO Member Societies, which will define this global initiative and provide the resources to sustain the effort throughout the year.

Through a multi-faceted WDHD 2017 campaign, The WGO seeks to achieve two main goals: firstly, to provide simple messages for the general public in order to assist them in understanding how IBD affects one's daily life and its importance in one's health. Secondly, to develop information for healthcare professionals - both the generalist and the specialist. Multiple informational pieces are planned and will be distributed worldwide; the first to launch being a facts and tips guide on living with IBD for patients and healthcare professionals, in multiple languages. The WDHD 2017 campaign is titled "Inflammatory Bowel Disease (IBD): Navigating Evolving Therapies in an Evolving Disease". Please join us in ensuring its success.

Sincerely,



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World Digestive Health Day 2017 Steering Committee

World Digestive Health Day (WDHD) 2017 is led by the following individuals representing a global view and expertise. The Steering Committee guides the course of the WDHD campaign, leading in the development of tools and activities, including the WGO Handbook on IBD.



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Meet Our World Digestive Health Day (WDHD) 2017 Partners

The World Gastroenterology Organisation (WGO) and the WGO Foundation (WGOF) acknowledge and thank the following WDHD 2017 partners for their contributions to the WDHD 2017 campaign, *“Inflammatory Bowel Disease (IBD): Navigating Evolving Therapies in an Evolving Disease.”*

WGO is extremely grateful for our partners’ efforts to advocate, promote and raise awareness for Inflammatory Bowel Disease (IBD) worldwide.



Crohn's and
Colitis Canada
Crohn et
Colite Canada



Diagnosis and Management of Inflammatory Bowel Disease (IBD) in Mexico and Central America



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Epidemiology

The incidence of IBD is now rising in developing countries and is increasingly considered an emerging global disease. Despite limited epidemiological data from developing nations, it is now clear that both the incidence and prevalence of IBD are increasing from some reports in referral centers and populations. The predominant IBD form is UC having a ratio of UC:CD of 4-10 to 1.

A study from the biggest referral hospital (Instituto Nacional de Ciencias Médicas y Nutrición) in Mexico reported that the frequency of new cases with UC increased over time. The mean number of new UC cases increased annually from 28.8 per 100,000 hospitalizations per year in the first period (1987 to 1996) to 76.1 per 100,000 hospitalizations per year in the second period (1997 to 2006) ($P < 0.00008$), an increase of nearly 3-fold (1). The age-group distribution of the patients at diagnosis was as follows: 21 to 30 years (37.1%); 31 to 40 years (25.5%); 51 to 60 years (12.9%); 41 to 50 years (10.6%); under 20 years (13.2%) and over 60 years of age (1.3%). The female to male ratio was nearly 1, suggesting that UC was not gender-specific. On the other hand, while much less CD is seen at this institution the incidence increased 4-fold from 1994 to 2008. The peak incidence was between 30 to 60 years old and females and males were equally affected. There are no data available from the countries of Central America.

Diagnosis

The diagnosis of IBD is based on a multifactorial approach, based on clinical history, physical examination, laboratory work-up, endoscopic and histologic data, and radiologic findings. The diagnosis approach is based on local and Pan American Crohn's and Colitis (PANCCO) guidelines recently published in 2017 (2).

Clinical features

Ulcerative colitis: Bloody diarrhea is the predominant symptom. Urgency of defecation and incontinence are common and disabling. Severe disease is manifested by a marked increase in frequency of defecation, nocturnal awakening for bowel movements..

Crohn's disease: Pain is often a feature and may reflect the site of intestinal disease, for example terminal ileal disease causing right lower quadrant pain. When the small bowel is involved in CD, malabsorption and consequent weight loss are common. Penetrating tissue damage may result in the formation of abscesses and fistulae that may cause increased or different pain, increased frequency or change in the nature of diarrhea and cutaneous discharge. Localized entero-enteric fistulae are often asymptomatic, but a fistula that bypasses a substantial length of proximal small bowel can cause malnutrition and significant diarrhea. Entero-vesical fistulae may present with frothy urine (pneumaturia) or fecaluria. Stenotic intestinal disease may result in subacute bowel obstruction. Perianal involvement with fissures and discharging sinuses and fistulae is common in CD, and is seen in about 10% of Mexican patients. CD of the esophagus, stomach and duodenum is rare, affecting 1.7% of Mexican CD patients.

Laboratory investigations

Routine blood count and biochemistry often provides evidence of ongoing inflammation including an elevated white cell count, platelet count, C-reactive protein (CRP), fecal calprotectin and lactoferrin as well as low serum albumin level. Anaemia may be seen and this can be due to chronic intestinal blood loss, vitamin B12 and folate deficiency in patients with CD or secondary to chronic inflammation (anaemia of chronic disease). B12 deficiency in Crohn's disease is secondary to ileal inflammation and loss of absorptive area and/or resection. There has been some interest in the use of serological markers in the diagnosis of IBD, particularly in differentiating UC from CD. These include perinuclear staining antineutrophil cytoplasmic antibodies (p-ANCA) and anti-Saccharomyces cerevisiae antibodies (ASCAs). The prevalence of p-ANCA was 51% in Mexican UC patients.

Endoscopy

Endoscopy is a cornerstone in the investigation of patients with IBD, enabling both direct vision of the intestinal mucosa and mucosal biopsy sampling for a histological diagnosis. IL-

Diagnosis and Management of Inflammatory Bowel Disease (IBD) in Mexico and Central America, continued.

eo-colonoscopy represents the most important and powerful test in the diagnosis of suspected IBD, and it is important to undertake early in the diagnosis to document disease extent and activity before starting any medical treatment. By the Montreal Classification, in the distribution of disease in Mexican UC patients included 59.1% with pancolitis (E3); 25.5% with left-sided colitis (E2); and 15.4% with proctitis (E1). The location of CD in Mexican patients was distributed as follows: ileocolonic (L3) in 49.1%; ileal (L1) in 28.4%; colonic (L2) in 11.2%; perianal disease in 9.4% and upper involvement (L4) in 1.7%. Deep enteroscopy is indicated in the diagnosis of CD when histology is required for the confirmation and exclusion of other pathologies.

In patients with suspected CD and negative ileo-colonoscopy and cross sectional imaging, capsule endoscopy could be the initial diagnostic modality (subject to availability) for the evaluation of the small intestine, in the absence of symptoms of obstruction or evident stenosis on cross sectional imaging.

Radiology

Plain supine abdominal radiography often provides evidence of fulminant colitis and should be used in the assessment of toxic megacolon in UC patients. CT and MRI cross-sectional imaging are very useful in patients with CD in order to identify disease activity as well as complications such as stenosis, abscesses and fistulae.

The availability of MR or CT enterography is still limited to a few diagnostic centers in Mexico and Central America, because of lack of availability of equipment and lack of expertise of the staff to interpret the tests. Abdominal ultrasonography in expert hands is a well tolerated, radiation-free imaging technique, particularly for examination of the small intestine and colon, and can guide interventional procedures, however, no expertise is available in hospitals from Mexico and Central America.

Histopathology

Histologic examination of endoscopic samples or resection specimens is a key step in the evaluation of IBD patients. It can also be used for the differential diagnosis as shown in table 1. A wide variety of microscopic characteristics must be evaluated to help establish the diagnosis of CD such as focal chronic inflammation, discontinuous crypt distortion, and granulomas. The microscopic criteria of UC includes widespread distortion of crypt architecture, mostly continu-

ous inflammation of the mucosa with basal plasmacytosis, with or without cryptitis and crypt abscesses, and marked depletion of goblet cells.

Table 1. Differential Diagnosis of IBD in Mexico and Central America

Ulcerative Colitis	Crohn’s Disease
Infectious diarrhea (Amoebiasis, Salmonella, Shigella, Campylobacter, Giardiasis)	Intestinal Tuberculosis
Bowel ischemia	Lymphoma
Diverticulitis	Drugs (NSAIDs)
Drugs (NSAIDs, antibiotics)	
Post-radiotherapy colitis	

Management

The mainstays of IBD treatment are 5-aminosalicylates, corticosteroids, immunomodulators and anti-TNF agents. We base our medical treatment on local approaches and PANCCO guidelines. The goals of treatment are to eliminate symptoms (induction of clinical remission), prevent flare-ups (maintain long-term clinical remission), and restore patients quality of life in the reduction of surgeries and hospitalizations as well as mucosal healing (2).

Table 2 shows the treatment options available for IBD in Mexico and Central America.

5-Aminosalicylate drugs

Sulfasalazine and mesalazine are available in Mexico and Central America for the induction and maintenance of remission in UC. Concomitant treatment with oral and topical 5-aminosalicylates is superior to oral 5-aminosalicylate alone, as first-line treatment for inducing remission in patients with mild-to-moderately active UC, with any extension beyond the rectum. The use of 5-aminosalicylate drugs is limited to a small proportion of patients with CD focused in those with colonic involvement and is not used for maintenance of remission.

Corticosteroids

Corticosteroids are the main agents used to induce remission in moderate to severely active UC and ileocolonic CD and response rates of 80% may be expected. They are usually ineffective for maintenance of disease remission. Budesonide at a dose of 9 mg/day is the therapy of choice for inducing remission in patients with CD with mild activity and ileal and right colonic disease. The use of oral systemic

Diagnosis and Management of Inflammatory Bowel Disease (IBD) in Mexico and Central America, continued.

corticosteroids is recommended for inducing remission in patients with extensive small bowel CD.

In patients with moderate-to-severe UC of any extent, the use of oral systemic steroids as first-line treatment is indicated for inducing clinical remission. The use of oral systemic steroids as second-line therapy in the induction

of remission of patients with mild-to-moderately active UC that are resistant to 5-aminosalicylates is recommended.

Immunomodulating agents

Azathioprine, 6-mercaptopurine (6-MP), methotrexate and ciclosporin are immunomodulating agents of established use in the treatment of selected IBD patients. The use of thiopurine immunosuppressants is recommended for

Table 2. Treatment options available in Mexico and Central America for UC and CD.

Drug	UC	CD	Available in Mexico	Available in Central America
Sulphasalazine	Induction and maintenance of remission	Only for induction and maintenance of remission in colonic location	Yes	Yes
Mesalazine			Yes	Yes
Budesonide	Not indicated	Mild activity in ileocolonic location	Yes	No
Budesonide MMX	Induction for mild UC	Not indicated	Yes	No
Systemic steroids (oral and IV)	Induction of remission	Induction of remission	Yes	Yes
Azathioprine	Maintenance of remission	Maintenance of remission	Yes	Yes
6-mercaptopurine	Maintenance of remission	Maintenance of Remission	Yes	No
Methotrexate	Not indicated	Induction and maintenance of remission	Yes	Yes
Cyclosporine	Induction and maintenance of remission	Not indicated	Yes	Yes
Infliximab	Induction and maintenance of remission	Induction and maintenance of remission	Yes	Yes
Adalimumab	Induction and maintenance of remission	Induction and maintenance of remission	Yes	Yes
Certolizumab	Not indicated	Induction and maintenance of remission	Yes	Yes, few countries
Golimumab	Induction and maintenance of remission	Not indicated	Yes	Yes, few countries
Vedolizumab	Induction and maintenance of remission	Induction and maintenance of remission	Yes in 2018	Yes in 2019
Ustekinumab	Not indicated	Induction and maintenance of remission	No	No

maintaining remission in patients with corticosteroid-dependent IBD. In patients with CD that achieve remission with systemic corticosteroids, thiopurines or methotrexate is used in these patients.

Methotrexate may be used in chronically active CD that is corticosteroid resistant or dependent. Remission rates of 40% may be achieved after 16 weeks therapy and methotrexate may have a faster onset of action than azathioprine/6-MP. The drug may be continued as maintenance therapy, with 65% of patients remaining in remission at 40 weeks. Methotrexate has been used less widely than azathioprine/6-MP, and tends to be used in suitable patients where these agents have failed or have not been tolerated due to side effects. Methotrexate is not effective in UC. The use of methotrexate is very limited in Mexico and Central America because lack of experience.

Ciclosporin is a calcineurin inhibitor and is used in severe acute UC that is not responding to intravenous corticosteroid therapy. It is rapidly acting and response rates of 60–80% are usually seen within 5 days. In acute severe UC, ciclosporin therapy can avoid emergency colectomy, whilst enabling an alternative immunomodulatory such as azathioprine to be commenced for maintaining disease remission. In Mexico and Central America it is used in only a few tertiary-care centers because of a lack of expertise or fear of its use in other centers.

Biologic therapy

Antibodies against tumoral necrosis factor alpha (anti-TNF-alpha), such as infliximab, adalimumab, and certolizumab pegol, are indicated in patients with moderate-to-severe CD that have been refractory or intolerant to treatment with corticosteroids and immunomodulators. Further, infliximab and adalimumab are effective in closing fistulas and maintaining that closure in patients with CD.

In moderate to severe UC, anti-TNF therapy (infliximab, adalimumab and golimumab) is indicated in patients with a lack of response or intolerance to treatment with 5-aminosalicylates, corticosteroids, or immunomodulators. In severe UC refractory to IV steroids in hospital infliximab is an option, as an alternative to ciclosporin to avoid colectomy. All anti-TNF therapies are approved and commercially

available in Mexico and Central America. Complications associated with immune drugs in IBD Mexican patients are shown in table 3 and are considered in the PANCCO guidelines (3).

Vedolizumab is a specific humanized monoclonal antibody that targets integrin $\alpha 4\beta 7$ (a variable surface glycoprotein expressed on the surface of circulating T and B cells), which interacts with the gut specific MAdCAM-1 adhesion molecule. This biologic therapy is already approved for CD and UC patients and will be commercially available during 2018 in Mexico and Central America.

Ustekinumab is a monoclonal antibody that blocks the p40 subunit of interleukin-12 and interleukin-23 that was recently approved for the treatment of CD patients in United States of America. This treatment is not commercially available yet in Mexico and Central America.

In conclusion, the incidence of IBD has increased in the last decade in Mexico and most likely in Central America. The diagnosis is based on the composite of clinical history, physical examination, laboratory work-up, typical endoscopic and histologic data as well as radiologic findings. The current management of IBD is focused on the administration of 5-aminosalicylates, corticosteroids, immunomodulatory and anti-TNF agents. Vedolizumab and ustekinumab are not commercially available yet in Mexico and Central America.

Table 3. Complications associated with immune drugs in IBD Mexican patients.

Corticosteroids	Immunomodulators	Anti-TNF therapy
Urinary tract infection (29%)	Leucopenia (1%)	Herpes zoster infection (1%)
Respiratory infection (16%)	Pancreatitis (0.003%)	Histoplasmosis (0.3%)
Osteoporosis (15%)	Lymphoma (0.0001%)	Cytomegalovirus (0.2%)
Candidiasis (5%)	Non melanoma skin cancer (0.002%)	Melanoma skin cancer (0.1%)
Diabetes (3%)		Tuberculosis (0%)
Tuberculosis (2%)		



Diagnosis and Management of Inflammatory Bowel Disease (IBD) in Mexico and Central America, continued.

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Diagnosis and Management of Inflammatory Bowel Disease (IBD) in Latin America



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Incidence / Prevalence in Latin America; and differences with the rest of the world

Over recent decades, newly industrialized countries in Latin America have documented a significant increase in the incidence of Inflammatory Bowel Disease (IBD); Brazil is one of them with 84% of the population living in urban centers, mainly in the South and Southeast regions. According to data from the Brazilian Institute of Geography and Statistics (IBGE) in 2008, the country has a high rate of racial miscegenation with 44% of the population self-reported as brown (mestizos), and has suffered perceptible

changes in eating habits shown by the increase of obesity in the general population. In Brazil, the incidence of IBD was 1 per 100,000 between 1986 and 1990, but from 2001 to 2005 the incidence of ulcerative colitis and Crohn's disease was 4.5 and 3.5 per 100,000, respectively. A Brazilian study, conducted in a region of the state of São Paulo, showed the increase in incidence that occurred in the last decade, and the change in the proportion between cases of Crohn's disease and ulcerative colitis was similar to what is happening in other countries of Latin America. The increased incidence was significantly higher among women.

Epidemiological studies in Latin America are scarce, but there are reports that regions such as Brazil, Argentina, Mexico and Chile have a higher prevalence of IBD. In the Northeast region of Brazil, a study showed that the majority of patients with IBD were miscegenated (67.9%), had a high educational level (62.4%), lived in urban areas (86.1%) and were less than 40 years of age (62.5%). A Chilean study of 716 patients showed that (71%) had ulcerative colitis, (27%) Crohn's disease and (2%) IBD-type unclassified. Females made up (58%) of the study, and the majority were also living in urban areas with an average age of diagnosis at 29 years.

There is not mandatory reporting of IBD in Latin America, which is why there is a lack of reliable epidemiological data. This also contributes to a delayed diagnosis of patients with IBD and a consequent increase in morbidity. In some countries, such as Mexico, the incidence of ulcerative colitis is considerably higher when compared to Crohn's disease, while in others, such as Brazil, Argentina, Uruguay and Chile, the difference is not as significant.

Diagnosis

Biomarkers and clinical and histological aspects

The initial evaluation of a patient with IBD is perhaps the most important. At that moment, the medical professional gets his/her first impression of the patient as well as their illness. Initially the diagnosis must be confirmed and all differential diagnoses considered. The diagnosis of IBD should be based on the correlation of clinical, laboratory, radiological, endoscopic and histological aspects. In the vast majority of Latin American countries there is a shortage of specialized professionals, as well as diagnostic resources, which makes an early diagnosis of IBD difficult.

Diagnosis and Management of Inflammatory Bowel Disease (IBD) in Latin America, continued.

With regard to diagnosis, the most used activity indices in Latin America are the Crohn's Disease Activity Index (CDAI) and the Harvey-Bradshaw Index (HBI) for Crohn's disease and the Mayo score and the Truelove & Witts Index for ulcerative colitis.

In Latin America, baseline exams, usually performed at the time of diagnosis, include complete blood count, electrolytes, renal function, liver function, inflammatory activity tests such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), iron kinetics, folic acid, and vitamin B12. The serological markers anti-Saccharomyces cerevisiae (ASCA) and anti-neutrophil cytoplasmic antibodies (ANCA) may be useful for the differential diagnosis between ulcerative colitis and Crohn's disease but not for IBD diagnosis, and are not available in all countries in the region.

Regular fecal tests are routinely performed to eliminate infectious, bacterial, viral or parasitic causes of diarrhea, especially *Clostridium difficile*, as well as fecal calprotectin - a simple, reliable and available test to measure disease activity. Both fecal calprotectin and *Clostridium difficile* fecal screening are not yet available in all countries in Latin America.

Intestinal tuberculosis is an important differential diagnosis that should be excluded in areas of high incidence. There are some tests for the diagnosis: tuberculin-purified protein derivative (PPD) skin test, serum PPD antibody test, interferon gamma assay (QuantiFERON-TB, T-SPOT, TB test). The interferon gamma release assay (IGRA) has high specificity for TB diagnosis in Latin America. The skin test is the most available test in most countries, and the least expensive one.

Histological analysis is very useful to compliment the diagnosis of IBD, but without other associated tests it has little value. The presence of incomplete granulomas, which raise the suspicion of Crohn's disease, for example, does not occur in more than 30% of the cases.

Endoscopy

Currently, endoscopic evaluation is the main test used in Latin America to detect, measure and monitor intestinal inflammation in IBD. As a rule, it is performed before starting any type of treatment. However, endoscopic evaluation has a high cost and is invasive and uncomfortable for the patient, which limits its use.

When Crohn's disease affects the proximal small intestine, not accessible by ileocolonoscopy or gastroscopy, the endoscopic capsule can be of great importance because it can detect lesions when the computerized tomography or magnetic resonance enterography leaves doubts. Unfortunately, the capsule is not available in many Latin American countries, and the cost of doing it is very high.

Some endoscopic advances such as chromoendoscopy allow a more precise detection and a better characterization of dysplastic lesions, and evaluates the severity of the disease in comparison to white light endoscopy. However, it is not commonly undertaken in most Latin American countries; besides availability, there is still a lack of consensus and guidelines on this subject.

Imaging tests

The emergence of cross sectional imaging techniques such as computerized tomography (CT) and magnetic resonance imaging (MRI) has progressively replaced conventional radiological studies in Latin America because the CT and MRI allow an overall assessment of the abdomen. Despite this, conventional radiological examinations, such as intestinal motility Rx, ultrasonography and abdominal tomography, still play an important role in the evaluation of IBD because they are available in the majority of radiology services and are low cost. The availability of MRI or CT enterography is still limited to a few medical centers in Latin America, and its reliability depends on the radiology team and their experience in interpreting the exam.

IBD Treatment in Latin America

Much like in the rest of the world, the treatment of IBD in Latin America has evolved in the last two decades. The 5-aminosalicylates, corticosteroids, and immunosuppressants remain available to treat IBD, and biologic therapies such as anti-tumor necrosis factor-alpha and anti-integrins are now part of the treatment arsenal. Even with the progress described, the countries of Latin America continue to lag behind developed countries in North America and Europe when it comes to treatment of IBD. The lag is due to the limited variety of medications available in Latin America and because the medications are difficult to access for most of the Latin American population.

In Brazil there was a recent mapping of the dispensation of drugs for IBD. The lack of or difficulty of obtaining the drugs was detected in (78.9%) of the Brazilian states; this diffi-

culty is found in (96%) of the public sector and (24%) of the private sector. Medications with the greatest distribution problem are mesalazine and azathioprine. With regard to access to biologic medications in Brazil, the main difficulty revolves around the need for drug optimization in cases of patients refractory to conventional doses, and also because some medications are only provided by the public sector, such as infliximab and adalimumab. In contrast, certolizumab pegol and vedolizumab can be used only by patients in Brazil with access to the private health sector, and are not yet distributed in the public sector.

High-cost medications provided by the Brazilian government are released in specific pharmacies. Their dispensation requires forms be completed by the prescribing physician, and complimentary tests must be attached to prove the disease. Often this process is time-consuming and the medication may not be released when the patient needs it. The following drugs are currently available through the public health sector for the treatment of Crohn's disease and ulcerative colitis: sulfasalazine, mesalazine, azathioprine and corticosteroids. In the case of Crohn's disease, if these medications fail, there is the option of anti-tumor necrosis factor infliximab and adalimumab available.

The objectives of treatment in Latin America are the same as elsewhere: clinical remission and healing of the mucosa, thus reducing the chance of complications, hospitalizations and surgeries. Achieving a significant improvement in the quality of life of patients with IBD is the main goal. Scheduling a colonoscopic follow-up at the desired time may be difficult, thus interfering with the ideal follow-up time.

Medications

1. Aminosalicylates

- Sulfasalazine and mesalazine (the latter available as an oral tablet, suppository and enema).
- They are effective in inducing and maintaining remission in patients with mild to moderate ulcerative colitis.
- Currently, they play a small role in the treatment of Crohn's disease; they can be used in mild cases where the disease affects only the colon.

2. Corticosteroids

- Their main function is to induce clinical remission during flares of exacerbation of the disease. Corticosteroids decrease inflammation and promote rapid relief of symptoms.
- This class of drugs is not indicated for the maintenance of remission in IBD due to the large number of side effects of its prolonged use. In addition, it does not enhance mucosal healing and does not promote improvement in cases of fistulas due to Crohn's disease.
- In patients with Crohn's disease of the distal ileum, budesonide may be used as the first choice.
- Steroids can be administered orally, intravenously or rectally depending on the severity and location of the disease.

3. Antibiotics

- This class of drugs has limited use in the treatment of IBD, being reserved mainly for the treatment of perianal and fistulizing Crohn's disease.
- The most frequently used antibiotics are metronidazole (imidazole) and ciprofloxacin (quinolone).

4. Immunosuppressants

- The most commonly used are thiopurines (azathioprine and 6-mercaptopurine).
- Thiopurines should not be used for remission induction due to their delayed onset of action. They can be used as a maintenance drug in patients, with ulcerative colitis or Crohn's disease, who have achieved remission with corticosteroids.
- Thiopurines can be used as monotherapy, and in combination therapy with anti-tumor necrosis factor (mainly infliximab).
- Patients taking thiopurines should be monitored for increased risk of infections and lymphoma (especially in the very young, the elderly, and/or male patients).
- There is also the possibility of using methotrexate for Crohn's disease, and intravenous cyclosporine only in cases of ulcerative colitis exacerbation.
- Tacrolimus is also described in the literature as a therapeutic option in Crohn's disease, but is hardly used for this purpose in Latin America.

Diagnosis and Management of Inflammatory Bowel Disease (IBD) in Latin America, continued.

5. Biologic therapy

- This class of medications is the most recent and effective option in the treatment of both Crohn's disease and moderate to severe ulcerative colitis. It can be the first line of treatment for patients with severe illness and fistulizing Crohn's disease.
- Due to its high cost, the use of biologic therapy in the treatment of Crohn's disease and ulcerative colitis can have a great impact on the economy of Latin American countries. This may influence the use and availability of these medications in countries such as Argentina, Brazil, Colombia and Mexico.
- Anti-tumor necrosis factor-alpha drugs (infliximab, adalimumab and certolizumab pegol) and an anti-integrin drug (vedolizumab) are available for use in Latin America, in IBD cases.
- In Brazil, only infliximab and the adalimumab are provided by the public health sector for Crohn's disease. Both medications are approved for use in patients with ulcerative colitis but they are not distributed in the public health sector due to lack of governmental regulation for the disease. Certolizumab pegol should soon begin to be provided by the public health sector for Crohn's disease. Vedolizumab is still reserved for those of the population with access to the private health sector.
- Anti-tumor necrosis factor-alpha and anti-integrin medications can be used in induction of remission and also in the maintenance phase. However, literature shows that anti-tumor necrosis factor-alpha medications have a faster onset of remission induction, so they would be more suitable for use in critically ill patients who need a more immediate response.
- There is a great concern regarding serious infections during the use of biologic therapy. In Latin American countries, infections such as tuberculosis are very prevalent. Therefore, an active search for latent infections in patients with IBD is required for the use of biologic medications.
- Other medications used in North American and European countries, such as golimumab (a subcutaneous anti-tumor necrosis factor medication with good results for treatment of severe ulcerative colitis) and

ustekinumab are not yet available in Latin America; the approval of both drugs in Brazil is expected shortly.

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Inflammatory Bowel Disease (IBD) in Africa



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In 2012 an important paper reported a map depicting the prevalence and incidence of UC & CD in the world by Molodocky NA, et al (1). The whole continent of Africa was coloured white (no data) except South Africa coloured blue (low risk) for both UC and CD.

In Africa it is still relatively rare, but incidence is increasing in a dramatic way. A comprehensive literature search using Midline, Emhare and African index medicine found a total of 67 publications (2). The majority of the publications are retrospective hospital based studies which generally underestimate the incidence and prevalence of the disease. All studies showed that IBD is rare in Africa.

In Sudan between 1990 and 2001 in a tertiary referral hospital in Khartoum 72 cases of IBD, 60 cases of UC and 12 cases of CD were reported (2). Both diseases were more common in men, in 2nd and 3rd decades of life. In a recent MD thesis study in another nearby tertiary referral hospital in Khartoum between 2006 and 2010 a retrospective study found 72 cases of IBD 42 (58%) were UC and 15 (21%) were CD, 15 (21%) were labeled indeterminate colitis most of cases were diagnosed in the last 3 years of the study (3). The same number of patients were seen in 10 yrs in the first report 1990 – 2001 and in 5 years, in the second report 2005–2010.

The causes behind the recent increase of IBD cases are not clear. Possible causes are:

1. Better awareness of these diseases by doctors.
2. Better diagnostic facilities especially easier access to endoscopy and computerized tomography scans (CT)
3. Changes in environment especially unregulated use of fertilizers and pesticides.
4. Increased use of antibiotics by doctors and patients who can get them over the counter, increased use of antibiotics by poultry farming etc.. Antibiotics used es-

pecially in childhood is associated with increased risk of Crohn's disease development.

5. The hygiene theory, exposure to parasites in childhood boost development of mucosal immunity and may prevent development of IBD. Better hygiene and less exposure to parasites in childhood, may enhance the development of diseases like IBD, asthma etc. A recent study showed that H Pylorii infection in childhood seems to protect against IBD.
6. Change in dietary habits especially the introduction of fast food in most big cities in Africa where young people see it as fashionable to eat fast food outside home.
7. Increase in cigarette smoking, tobacco though may protect against UC but worsen the clinical presentation of CD and bring it to the doctors attention. International tobacco companies are now intensifying their marketing in developing countries after being squeezed in Europe and America.
8. It seems logical to think that a hitherto unknown organism or organisms maybe responsible for IBD. Mycobacterium avium paratuberculosis is suspected by some but based on anecdotal reports.

Clinical Presentation of IBD in Africa

The clinical presentation in Africa is similar to the presentation in the West. In ulcerative colitis one has to rule out bacterial and parasitic causes of bloody diarrhea eg amoebiasis, schistosomiasis. In CD the main differential diagnosis is intestinal tuberculosis and it could be very difficult to differentiate between the two even under the microscope.

In addition to simple stools examination, endoscopy and imaging especially CT despite their relative high cost and need of expertise are best modalities to diagnosis CD and UC in Africa. Magnetic resonance imaging is more expensive and the expertise to read MRIs in Africa is limited. Wireless capsule endoscopy is used in small intestinal CD despite the small risk of capsule retention. Double balloon entoscopy is used in our unit to dilate some jejunal strictures but they tend to recur. The table shows how to differentiate CD from intestinal tuberculosis.

Treatment of Ulcerative Colitis

A Simple Practical Classification (4) of UC activity is helpful in planning treatment:

1. Mild disease (up to four bloody motions daily with no systemic toxicity). Moderate disease (4 – 6 bloody motions per day with minimal toxicity).
2. In the above two categories: Aminosalicylates (Sulphasalazine, Mesalamine) are best drugs for induction and maintenance of remission. Patients with proctitis and left sided colitis can be given in addition to oral mesalamine, mesalamine suppositories or enemas, however both are expensive. Steroids enemas are cheaper because they can be prepared by the local pharmacist and are effective in induction of a remission. Oral mesalamine is better tolerated by patients but it is far more expensive than sulphasalazine.
3. Severe colitis more than 6 bloody stools daily plus signs of toxicity eg fever, tachycardia. Corticosteroids either oral or parenteral are best for these cases, when they improve they can be shifted to aminosalicylates. If they could not be weaned off steroids, azathioprine is added while withdrawing steroids gradually. Azathioprine is cheap and effective for long term maintenance. We rarely use methotrexate because of high toxicity.
4. Fulminant colitis more than 10 bloody stools, continuous bleeding, abdominal tenderness, colonic dilatation on X-ray abdomen. These patients need admission, intravenous corticosteroids if no response, ciclosporine, tacrolimus or infliximab, if available are effective. These patients need co-management with a surgeon.

The major issue in treating ulcerative colitis in Africa is that, the cheapest and readily available drugs are corticosteroids and are continuously used by patients with devastating side effects.

Treatment of Crohn's Disease

Trial of mesalamine can be undertaken in colonic and ileo colonic crohn's disease but usually not effective especially in isolated colonic crohn's disease. Corticosteroids are best drugs and they are usually combined with azathioprine. If the patient responded corticosteroids are gradually withdrawn and patient is maintained on azathioprine. Some patients benefit from addition of antibiotics eg metronidazole or ciprofloxacin. Azathioprine has rather dangerous long term effects eg hepatosplenic lymphoma but we have not seen it. In a long follow up study of patients with IBD from South Africa azathioprine is found to be relatively

Inflammatory Bowel Disease (IBD) in Africa, continued.

safe in black Africans. In severe cases of crohn's disease, fistulizing crohn's disease biological agents eg Infliximab or adalimumab though very expensive and not available in most African countries, can be tried.

Surgery is life saving in patients presenting with obstructive symptoms or not responding to the above treatments. The majority of patients with CD in Africa are diagnosed at laparotomy. Nutritional need of IBD patients need to be monitored carefully, milk is usually stopped during flare ups but most patients tolerate normal diet rich in protein. Parenteral nutrition and elemental diet are very expensive and needs trained teams. A trained IBD nurse is a good investment.

IBD should be taken seriously as it has significant social costs, these are young people, who can't work full time, have comorbid psychiatric conditions like depression and social withdrawal.

WHO and other donors should help Africa to treat IBD as they did in HIV.

To understand IBD in Africa we need more basic research and more community studies.

A promising start is the South African Gastroenterology Society (SAGES) recent sponsorship of an inflammatory bowel disease registry in South Africa.

Differences in Clinical Presentation of Intestinal Tuberculosis and Crohn's Disease (Adapted from Ref. 4)

Clinical Presentation	Tuberculosis	Crohn's Disease
Age	Age 3rd – 5th decade	Younger age 2nd – 3rd decade
Sex	Males predominant	Males predominant
Abdominal pain	Generalized	More often localized to right iliac fossa
Fever	Common	Uncommon
Diarrhea	Common, watery	More common, watery occasionally mixed with blood
Weight loss	Significant	Common
Anorexia	Common	Less common

Inflammatory Bowel Disease (IBD) in Africa, continued.

Upper GI symptoms	Rare	Common
Perianal disease	Rare	Common, 50% of cases
Imaging		
X-ray Chest	TB changes in up to 50% of cases	Usually normal
Barium Studies	Stricture dilated loops	Strictures, fistula tracts
CT	Bowel wall thickening, stricture, lymphadenopathy necrotic lymph nodes diagnostic	Bowel wall thickening, strictures, lymphadenopathy
Colonoscopy		
Apthous ulcers	Rare	Very common
Ulcer	Transverse	Longitudinal
Cobble stone appearance	Occasional	Found in up to 75% of cases
Ileocecal valve	Patulous	Fibrotic
Laboratory Tests		
ESR and CRP	Both elevated	Both elevated
Histopathology		
a) Granulomas	Common Holy grail	Common and giant Absent
b) Granuloma with caseous necrosis		
T spot test	positive	Negative
QuantiFeron test	positive	Negative
Tissue TB PCR	positive	Negative

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Epidemiology and Special Issues of Inflammatory Bowel Disease (IBD) in Turkey



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Epidemiology

The pathogenesis and etiology of IBD is incompletely understood. Combined genetic and environmental factors play a role in the etiology of these complex disorders. This

results in significant changes among different geographical regions. The incidence rates of, UC and CD seem to have stabilized in the western world whereas it continues to rise in developing countries like Turkey (1).

Turkey is a so – called bridge between east and west in many fields, just like in IBD. The rapid urbanization process observed in the last decades resulted in increased incidence and prevalence rates of IBD. There are a few hospital and regional based studies and two well designed multi – centric studies on the epidemiology of IBD in Turkey (3 – 10). Table 1 summarizes the data collected from these studies.

According to these figures, the prevalence and incidence of UC are 22,9 – 31,8 and 1,8 – 4,58 per population of 100.000, respectively. Those of CD are 7,56 – 12,5 and 0,69 – 2,98 per population of 100.000, respectively. These figures are between those evident in the industrialized and underdeveloped parts of the world. On an annual basis dating abck to 2007 there is an upward trend for both the adult and pediatric populations (Fig 1*).

Table 1. Epidemiological data gathered from major studies among Turkish population.

Author (ref) Years encompassed	N	UC/CD %	Prevalence (/105)		Incidence (/105 per yr)		Mean Age(yr)		Sex (M/F)	
			UC	CD	UC	CD	UC	CD	UC	CD
Özin Y (10) 1993-2007	702	72,2/ 27,8	-	-	-	-	46,2	40	1,2	1,6
Tözün N (8) 2001-2003	877	75,3/ 24,6	-	-	4,4	2,2	42,6	37,4	1,3	1,3
Dağlı U (9) 2004-2007	3954	74/ 25	25,5	7,7	2,6	1,4	38,4	34,3	1,27	1,24
Can G (7) 2004-2013	223	71,7/ 28,3	31,8	12,5	4,58	2,98	46,1	44,6	1,28	2
Tezel A (4) 1998-2013	358		22,9	7,56	1,8	0,69	47,1	42,5	1,3	1,2

Epidemiology and Special Issues of Inflammatory Bowel Disease (IBD) in Turkey, continued.

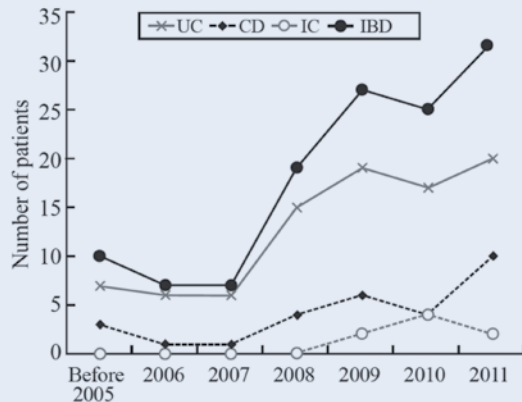


Fig. 1. Annual number of new patients with inflammatory bowel disease (IBD). UC: ulcerative colitis; CD: Crohn's disease; IC: IBD-unclassified.

* Taken from ref6.

A slight male predominance is seen both in UC and CD cases. In most studies of CD coming from moderate to high endemic areas, there is a female predominance, however in low endemic areas, male predominance may be seen. Age distribution of disease incidence in Turkey is bimodal in accordance with other countries. Most of the patients have urban residence (78% for CD, 75% for UC). Family history is 1,6 - 8,3 % which seems to be lower than in industrialized countries. As far as the clinical characteristics of the diseases are concerned, Table 2 shows a comparison between Asia, Turkey and Western countries.

As a result, the prevalence of IBD in Turkey is similar to Asia. UC is seen more commonly than CD. Most common clinical presentations are ileocolonic for CD, and left sided colitis for UC. Family history is of less importance than in the West. Rates of colorectal cancer and extra - intestinal manifestations are low.

Special issues

Main issues in the management of the IBD patients in Turkey are related to the differential diagnosis. There are relatively common conditions and diseases in the Turkish population, which may cause diagnostic challenges to the physician.

Behçet's syndrome

Behçet's syndrome (BS) is a systemic vasculitis that is comprised of recurrent oral and genital ulcers and uveitis

Table 2. Clinical features of IBD, among different sites of the world.

Variable	Asia	Turkey	Western World
Sex	D	M>F	F>M
		M=F	M=F
Age of onset (yr)	CH	20-30	20-30
	UC	30-40	20-50
CD predominant phenotype	Ileocolonic Perianal Disease	Ileocolonic	Similar distribution
UC predominant phenotype	Localization similar to west	45 % left sided colitis	30% proctitis, distal and extensive
Extra-intestinal manifestations (%)	6-14 PSC (0-1%)	13,8-21,7 PSC (0,9-1,2%)	21-41 PSC (2-7%)
Colorectal Cancer (%)	0-1.8	1.1	3-5
Family History(%)	0-3	4,2-4,3	10-25

by description. BS may affect many organ systems. Gastrointestinal involvement has been reported in up to 60 % of cases in different patient cohorts (12). BS can affect any part of the GI tract, but the terminal ileum and cecum are sites of predilection. It causes single, deep, large ulcers with tendency to cause bleeding and perforation. These lesions have characteristics resembling IBD – mainly CD – with features of vasculitis (13). 8,7 % of cases may have signs of inflammation and vasculitis, even in endoscopically normal appearing mucosa at terminal ileum, so biopsies should be taken from the sites of predilection (Unpublished data). Endoscopically, CD ulcers tend to be apthous and multiple, with cobble stone formation, which is important for the differential diagnosis. Another diagnostic challenge is that in more than one third of BS patients referred to endoscopy for GI issues may in fact have other etiologies. Among these, NSAID enteropathy, antibiotic associated colitis, intestinal tuberculosis, diverticulitis or radiation injury need mentioning. Calprotectin levels are also elevated in BS as in CD.

Epidemiology and Special Issues of Inflammatory Bowel Disease (IBD) in Turkey, continued.

Treatment consists of 5-ASA in mild cases, and azathioprine (AZA) or mycophenolate mofetil (MMF) with corticosteroid induction in moderate to severe enteric – Behçet cases. Anti – TNF should be reserved for refractory cases.

Amebiasis

Amebiasis is mainly seen in underdeveloped countries due to poor sanitation. Studies reveal a link between amebiasis and IBD, mainly UC. Patients present with severe diarrhea. It is more commonly seen in the inflamed milieu of IBD, furthermore it can cause flares in the course of the disease. In the large multi – center cohort from Turkey, amebiasis was detected in 17,2% of UC and 1,3% of CD patients (8). This high rate of amebiasis is relevant at first presentation, and also exacerbations of UC. One ongoing debate here is that most of these cases may be due to saphrophite amoeba like *E.dispar*. To rule out pathogenic amebiasis that requires treatment, stool Ag test for *E.histolytica* should be used in the workup(14). Recent data suggest that, there is a decline in amebiasis in Turkey due to higher standards of sanitation.

Familial Mediterranean Fever (FMF)

Patients with FMF can present to the clinics with chronic diarrhea due to chronic autoinflammatory process, as a side effect of colchicine – a potent antimetabolic agent –, secondary to NSAID enteropathy or intestinal amyloidosis due to poorly controlled disease (15). To complicate the issue even further, MEFV variation frequency was higher in IBD (25,5%) patients (28% in UC and 22,6% in CD) compared with controls (9,9%, $p=0.006$). This means that, FMF – associated MEFV variations are associated with an increased risk of IBD in Turkish patients ($OR=4.4$, $p=0.001$)(16). In 64% of FMF cases there are ulcers or erosions mainly at jejunal segments, and in 24% they can be found in ileal segments. Capsule endoscopy and endoscopic pathologic assessments can be helpful for discrimination and further evaluation of these cases.

Tuberculosis

Intestinal Tuberculosis (IT) is still commonly seen in developing or underdeveloped countries, including Turkey, although the incidence is declining in recent years (17). Involvement of less than 4 segments, a patulous ileocecal valve, transverse ulcers (in contrast to longitudinal ulcers of CD), fibrous scars and pseudopolyps are more commonly

seen in IT than CD (18). If pathological evaluation fails to reveal acid fast bacilli serological as well as PCR based assays, should be used in suspected cases — to prevent potential catastrophic results due to immunosuppressive treatment for IBD misdiagnosis.

Conclusions

The prevalence and incidence of UC are 22,9 – 31,8 and 1,8 – 4,6 per population of 100.000, respectively. Those of CD are 7,6 – 12,5 and 0,69 – 2,98 per population of 100.000, respectively. Presentation with UC is more common in Turkey, than CD. Extra – intestinal involvement and cancer is less commonly seen. Behçet's syndrome, amebiasis, FMF, and tuberculosis are potential challenges in the differential diagnosis and management among Turkish patients.

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Diagnosis and Management of Inflammatory Bowel Disease (IBD) in India: Challenges and the Way Ahead



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Background

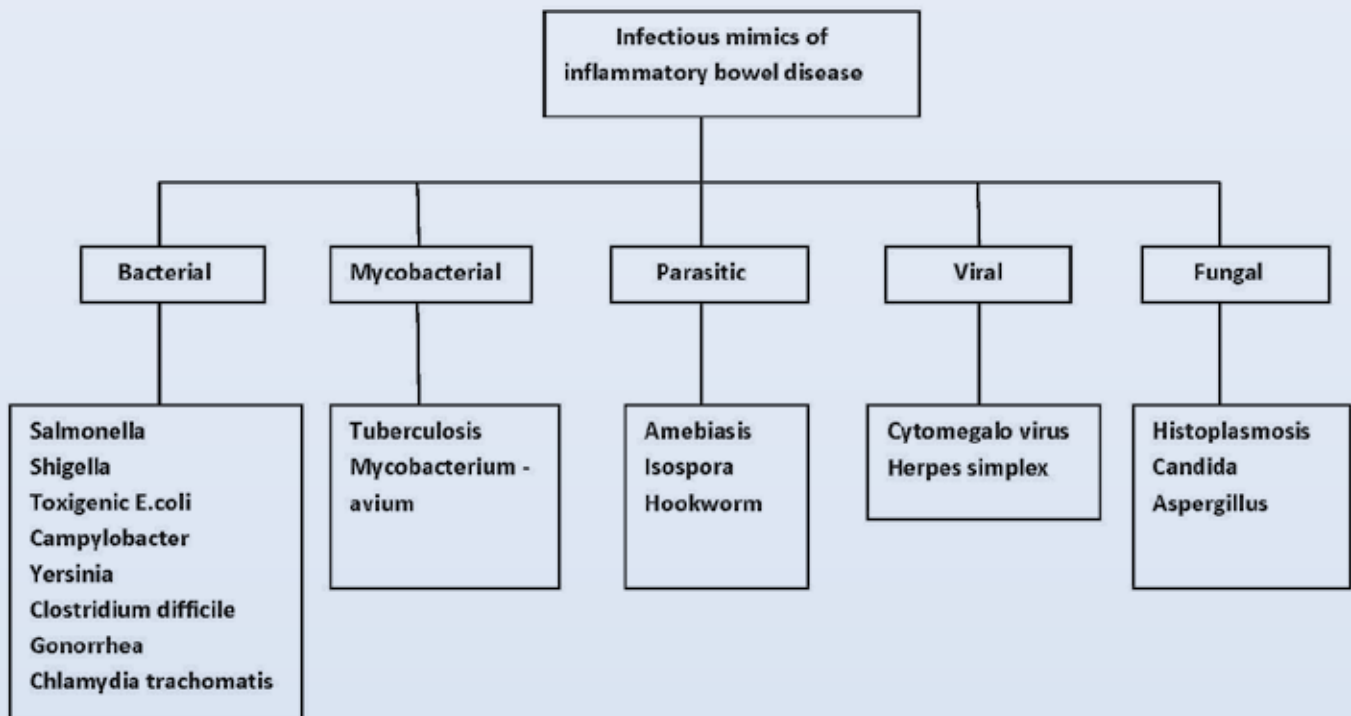
India is a vast land of remarkable diversity. There is a large population of people belonging to multiple races, varying genetic makeup, diverse cultures, dietary preferences and belonging to different socioeconomic environments. Traditionally this has been a country where infectious diseases predominate.

Inflammatory Bowel Disease was believed to be rare in India. The first report of ulcerative colitis (UC) was in 1933 when Chopra et al reported 6 cases of non infective colitis which were not amoebiasis and biopsy was nonspecific.

The first reports of Crohns disease (CD) included patients operated for a stricturing ileocaecal disease. The incidence of IBD in India remained low even up to the eighties with only a limited number of publications. There were some reports of ulcerative colitis primarily from north India. Crohns disease was rare. However there were reports of a high prevalence of IBD in the Indian migrants to the west including to the US, UK, Canada or even other South Asian countries.

After the 1980s there has been a steady increase in the incidence of inflammatory bowel disease for both ulcerative colitis and Crohns disease across Asia including India. The changing environment, more affluent lifestyles and increasing modernization and westernization has been attributed for this rise particularly in view of the earlier migrant population studies. In fact, immigration studies initially from the UK and now from the US, Singapore and Malaysia are reporting that second generation immigrants from the Indian subcontinent have the same or even higher incidence of IBD compared to the background population of the country.

Table 1.



Diagnosis and Management of Inflammatory Bowel Disease (IBD) in India: Challenges and the Way Ahead, continued.

Table 2.

Comparative clinical features of IBD				
Country Factors	India		Australia	
	UC	CD	UC	CD
Median Age (yr)	37	33	42	34
Gender (M:F)	1.56:1	2.64:1	1:1.2	1:1.1
Smokers	7%	6%	8%	10%
Disease location				
L1		30%		31%
L2		24.40%		24%
L3		41.40%		45%
L4		4.26%		5%
Disease behaviour				
B1		69.46%		88%
B2		20.87%		10%
B3		9.70%		2%
Perianal		8.20%		12%
Disease extent				
Proctitis	19%		32%	
Left sided colitis	50.10%		27%	
Extensive colitis	30.88%		41%	
Treatment at initial diagnosis				
5ASA	96.20%	40.80%	86%	71%
Corticosteroids	31%	49.13%	50%	67%
Immunosuppressive	0%	10 %	0%	14%
Biologics	0%	0%	0%	0%
Antibiotic	92.60%	95.90%	0%	21%
Surgery	4.56%	16.30%	5.90%	14.30%
Positive family history	4.34%	4.13%	17%	
EIM				
Joints	26.16%	21.73%	3.60%	
Uvietis	4.09%	3%		
Skin	11.39%	9.53%	3.60%	

IBD does appear to be an emerging disease in this part of the world. UC is more prevalent than CD. The Indian Society of Gastroenterology Task Force reported a ratio of approximately 2:1. However the trends indicate rising CD, particularly in the Southern part of the country with an UC: CD ratio of 3:2 and lower. This is similar to epidemiological studies from the west where the incidence of UC preceded the increase of CD by a few decades but then CD incidence rates rose compared to that of UC.

IBDs are chronic, life-long diseases. Extrapolated data based on prevalence and the population suggests that the overall burden of IBD in India is already amongst the highest in the world today. The increasing burden in an emerging world country like India where infectious diseases are rampant has significant implications. IBD is not considered a public health problem in light of a much higher prevalence of infectious diseases. There is a limited access to health care facilities combined with a poor awareness of the disease. There are unique diagnostic and management challenges for an emerging disease in an emerging and developing country like India.

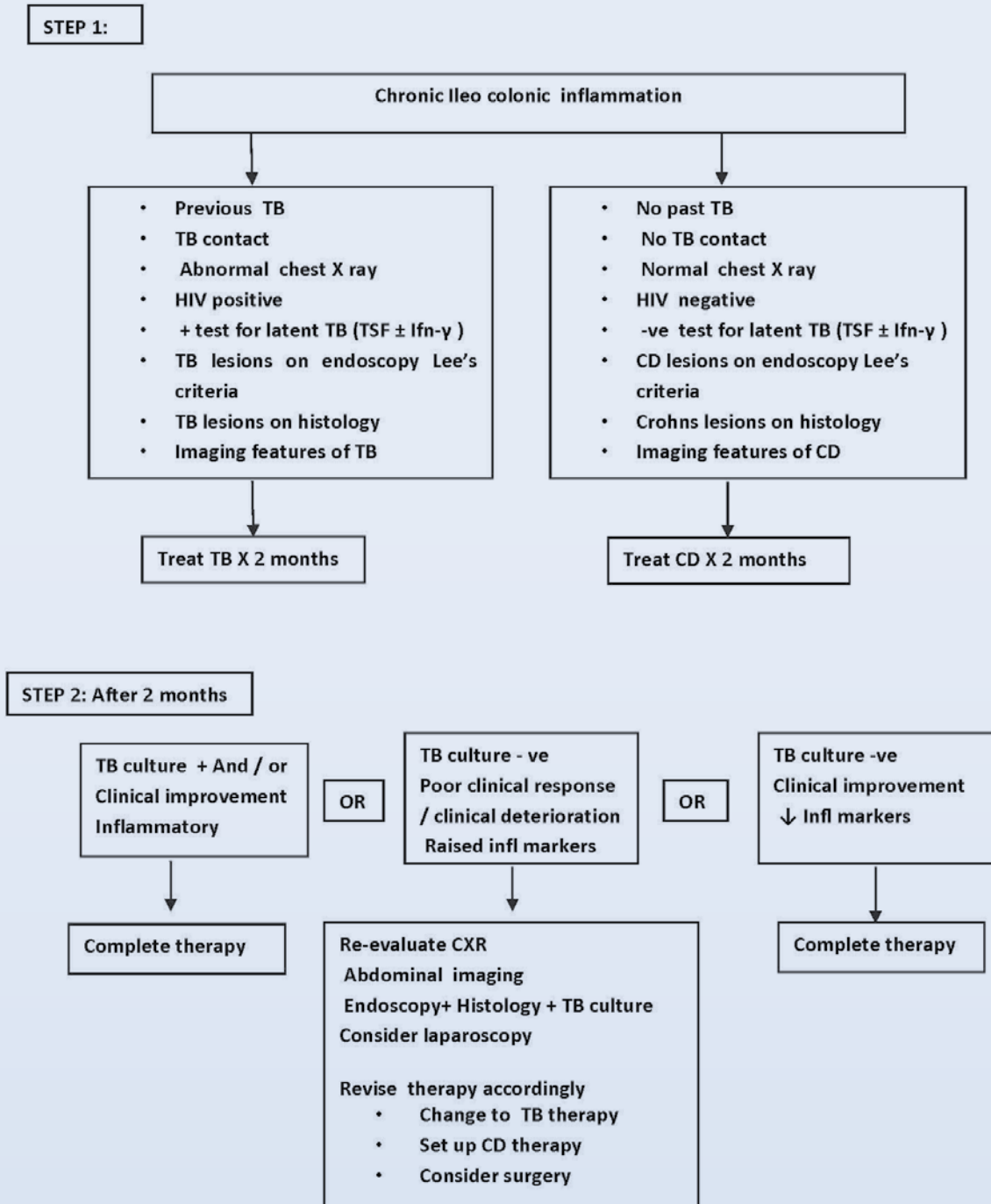
Diagnosis of Inflammatory Bowel Disease: The Indian Perspective

Inflammatory Bowel Disease (IBD) is a complex chronic disabling disease resulting from the interaction of autoimmune, genetic and environmental factors. The demographic and phenotypic manifestations of the disease vary between geographic locations. Accordingly the disease characteristics differ between Asian IBD and that of the west. This variability together with the prevalent socioeconomic conditions and availability of health care facilities results in variations in practice patterns and management approaches.

As such, there is no gold standard for the diagnosis of IBD by disease presentation. In India, the presence of infectious mimics of IBD delays the diagnosis and accurate assessment of the disease (Table 1).

The first attack of bloody diarrhea is often labeled as “acute infectious gastroenteritis” and usually receives an empirical course of antibiotics to treat for the very common amoebic infection. These antibiotics are available OTC as well and often are used as a self-medication before a visit to the physician. Similarly recurrent episodes of non-bloody diarrhea may receive multiple courses of antibiotics before reaching a physician and even by the general

Table 3. Management approach for the TB vs CD conundrum



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physician before further investigations. Referral to a GI specialist typically occurs only after recurrent attacks or in unresponsive cases. This results in an inordinate diagnostic delay which is both patient and physician related.

There are no true population based registries in India. Most of the data come from specialty hospitals which does have its limitations. We compared our registry data with that from the west (Australia)(Table 2). The symptom profile and diagnostic tools do not appear to differ much between India, other Asian countries and the west.

Early studies on UC had reported mild disease responding to mesalazines and corticosteroids but the last two decades have shown an increase in severity of the disease. However the incidence of acute severe colitis, complications and need for surgery still appears to be low compared to the western data. The incidence of colitis associated cancer was also considered low but a few recent studies have shown a rising number of cases particularly after 20 years of disease. This could be related to the increasing severity of cases with a higher number of patients with pancolitis or larger number of cases with >20yrs of illness.

Patients with CD normally present around the third decade with a male predominance. We found the extent of disease to be comparable to that of the west with ileocolonic disease being the most common in more than 40%of cases (Table 2).

The primary difference appears to be the higher incidence of extra intestinal manifestations (EIM) in the Indian population. 21% of patients in our cohort suffered from EIM . The incidence of familial IBD is significantly lower (4.25%) than the west (17%) but similar to that reported from other Asian countries including China, Japan and Korea.

Colonoscopy with biopsy for histopathology is the most commonly used diagnostic tool. Small bowel evaluation is usually done for select cases and includes enteroscopy as well as capsule endoscopy.

Amongst the radiological investigations, an initial ultrasound screening is often the first choice. This appears to be the cost effective option. CT scan/CT Enteroclysis of the abdomen is done only in few patients for severe abdominal pain, a suspected abscess, prior to a surgical intervention or non-response to first line medication. MRI facilities are

not available widely across the country and MRI/MRE is therefore restricted to select specialized centers only.

Biomarkers including ANCA, ASCA are available. However ANCA positivity has been reported in only up to 32% of UC and 10% of CD patients in India. ASCA levels have also not been able to differentiate between tuberculosis and CD with certainty. Consequently these biomarkers are not used much in clinical practice.

The TB vs CD dilemma

The increasing incidence of IBD over the last two decades in India where tuberculosis (TB) is endemic often results in a diagnostic dilemma between CD and intestinal tuberculosis. The clinical, radiologic, endoscopic and histological findings can be inconclusive particularly for ileocaecal disease.

A high rising or evening rise of temperature favours intestinal tuberculosis in the absence of any intra-abdominal abscess. A past history or family history of tuberculosis could alert towards possible TB. Caseation and positive TB cultures from tissues are diagnostic of TB but are found in only 10% and 2-3 % of cases respectively. Similarly the presence of chronic diarrhoea, blood in stools, perianal disease, fistulization and extraintestinal manifestations are more common in patients with CD. However there is often a symptom overlap and treatment for CD with steroids can actually cause a flare up of TB.

Consequently, nearly 30% of patients receive an empirical anti-tubercular therapy (ATT) before the diagnosis of CD is confirmed. The dilemma is further compounded by the fact that some patients with CD do show an initial clinical response to ATT. It is not clear whether the two diseases could coexist.

A routine management algorithm in cases with chronic ileocaecal ulceration is as follows (Table 3).

Management of Inflammatory Bowel Disease: The Indian Perspective

The standard step up therapy is followed for the management of IBD. The top down approach with biologics first as advocated by some studies is often not practical in India. The primary reasons being the prevalence of latent TB and the high cost of the drugs.



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Generally ulcerative colitis (Table 1) even pancolitis follows a benign course with good response to medications. Steroids are used intermittently either for induction of remission or for the treatment of flares. They are tapered off within a few weeks and maintenance is on mesalamines usually 2.4gm /day. Azathioprine is the most common immunomodulator used particularly for steroid dependant or steroid resistant cases or for recurrent relapses. TPMT testing is available and used at select centers only. Dosage is usually titrated and stepped up over weeks after monitoring blood profile including leucocyte counts. Methotrexate is not used much except for Azathioprine intolerant or non-responsive cases. The use of biologics is very limited for UC and a surgical option is often considered in patients with steroid refractory, intolerant or dependant ulcerative colitis. However use of biologics vs the surgical option is often a delicate balance between the cost differences, availability of surgical expertise and stoma care issues. Additionally many patients would prefer to defer surgery till absolutely necessary. Most surgeons prefer a three stage colectomy with pouch procedure.

The management of CD in India is only after tuberculosis has been confidently ruled out or after non response to empirical anti-tubercular therapy. Corticosteroids have a pivotal role in management and have been found to be effective in inducing remission. Immunomodulators are added for severe disease with high risk factors including small bowel disease or for recurrent relapses. Thiopurines are generally used. The problem of long term maintenance with thiopurines is the need for monitoring for side effects and the development infectious complications including tuberculosis due to immunosuppression. Methotrexate is used only in select cases not responding or intolerant to Azathioprine. 5ASA preparations are still commonly used for maintenance despite current evidence suggesting limited efficacy.

Infliximab is the only biologic approved for IBD in India. Vedolizumab and Golimumab are scheduled for release later this year. Biologics are expensive and often unaffordable. Biosimilars to infliximab and Adalimumab have recently been introduced to the Indian market. The advent of these biosimilars with lesser cost and comparable efficacy would perhaps increase and optimize the usage of biologics here. Around 2.53 % of our patient cohort is on maintenance biologics which is much less than that of the west. It is difficult to predict whether it is due to the affordability

factor alone or the disease course itself is milder here contributing partly to the limited usage.

The trend and research in India is now to develop low cost treatment options. Faecal transplantation for resistant UC, stem cell therapy for difficult CD have been used in select centers. We use autologous mesenchymal cell therapy for patients with complex perianal CD. The initial results appear good with healing of fistulas. A novel bioenhanced curcumin has recently been used as an adjunct therapy for induction of remission in mild to moderate ulcerative colitis with a significant improvement of symptoms compared to mesalamine alone. These low cost treatment options may be the next generation treatment for IBD in India.

IBD in India: The way ahead

IBD in India is on the rise. The large population of the country together with the rising incidence is expected to lead to a high burden of disease. It is affecting the young active age group and is associated with high morbidity. Moreover 70% of the Indian population is based out of the villages with poor access to specialized health care.

The challenges of treatment here extend over and above the diagnostic dilemmas with other infectious diseases. This includes the lack of awareness of the disease, poor accessibility to physicians or hospitals and a lack of adequate medical insurance. As the disease increases it is necessary to optimize the management of this disease balancing between the severity of disease and the cost of treatment.

There are very few dedicated IBD units in the country. A multidisciplinary integrated approach towards the treatment of IBD including not only the surgeon but also the rheumatologist, ophthalmologist, dermatologist, pathologist and radiologist is required both in the public and private sectors.

Indian IBD is emerging as the country moves towards westernization with changing environment and lifestyles. This provides an ideal setting for research to identify the etiopathogenetic factors of the disease. Additionally the cost of treatment needs to be reduced and the search for low cost yet effective treatment options for IBD is the need of the hour not only for India but globally.



*Diagnosis and Management of Inflammatory Bowel Disease (IBD) in India:
Challenges and the Way Ahead, continued.*

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Diagnosis and Management of Inflammatory Bowel Disease (IBD) in Hong Kong SAR



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Epidemiology of IBD in Hong Kong and China

In the past, inflammatory bowel disease (IBD) was a rare disease in Hong Kong. However, in recent years, there is a marked increase in the trend for both the prevalence and incidence of IBD in Hong Kong. In a territory-wide population-based IBD study in Hong Kong, the adjusted prevalence of IBD, Ulcerative Colitis (UC) and Crohn's Disease (CD) per 100,000 individuals were 44.0, 24.5 and 18.6, respectively (1). The age-adjusted incidence of IBD per 100,000 individuals has increased from 0.10 in 1985 to 3.12 in 2014 (1). Although the incidence of IBD in Hong Kong is still significantly lower than that in the West, it is the second highest amongst 8 Asian countries and areas across Asia. (2). The situation is similar in mainland China. In a prospective population-based incidence study carried out in a major city in mainland China, the age-adjusted incidence for IBD, UC, and CD were 1.96 per 100,000, 1.45, and 0.51, respectively (3). There has also been a shift in the types of IBD in Hong Kong. UC was the predominant disease in the past but the UC to CD incidence ratio has reduced from 8.9 to 1.0 over 30 years (1), suggesting that the incidence of CD is rising at a more rapid rate in recent years. However, such an observation was not seen in mainland China (3).

IBD can be as severe or more severe in Hong Kong and mainland China than in the West. Strictureing or penetrating disease was found in 41% and perianal disease in 25% of patients with CD (1) in Hong Kong while strictureing and

penetrating disease were found in 29% and 25% of CD patients at presentation in mainland China respectively (3). Gastroduodenal involvement of CD was found in 2% of CD patients in Hong Kong (4). Among those with UC, 34.5% had proctitis, 32.0% had left-sided colitis, and 33.5% had extensive/total colitis at diagnosis (1). Cumulative rates of surgery for CD were 20.3% at 1 year and 25.7% at 5 years, and the corresponding rates for UC were 1.8% and 2.1%, respectively (1).

Diagnosis of IBD

Tuberculosis is prevalent in Hong Kong and intestinal involvement of TB is not rare. Differentiating CD and intestinal tuberculosis (ITB) remains challenging. Both diseases share similar clinical, pathologic, radiologic, and endoscopic findings. The gold standard criterion to differentiate ITB from CD is by the detection of acid fast bacilli (AFB) on histology, smear, and culture of intestinal biopsy. However, the use of these methods is limited by the poor sensitivity and specificity of detection of AFB on smear and the time consuming nature of AFB culture. The sensitivity of ITB diagnosis can be enhanced by the use of TB polymerase chain reaction, however, the specificity is variable. In some cases where diagnosis is still in doubt, empirical TB treatment may be given and ITB can be diagnosed based on assessment of response to anti-TB therapy (5). Up to 14% of ITB cases were diagnosed based on response to TB therapy in Hong Kong (6). Recent data have shown that the combination of interferon-gamma releasing assay (IGRA) and anti-Saccharomyces cerevisiae antibody (ASCA) may be useful as a supplementary diagnostic tool with high specificity (7). In Hong Kong, we employ both IGRA and ASCA in patients with unclear initial workup before starting empirical anti-TB therapy.

Behcet's disease (BD) with gastrointestinal involvement is another differential diagnosis that has to be considered. Up to 10% of patients with Behcet's syndrome have gastrointestinal involvement (8). Patients with BD are more likely to have extra-intestinal manifestations and fever; endoscopically focal involvement, ileocecal valve deformity, solitary ulcers, large ulcers (ulcer size > 2 cm), and circumferential ulcers were more common in intestinal BD patients (9).

Other alternative diagnoses that must be excluded when considering CD include infectious enteritis or vasculitis

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Management of IBD

Generally, an Individualized approach according to risk factors is used for the management of IBD in Hong Kong. Early use of biologics is employed in patients with poor prognostic risk factors or rapid disease progression, namely, young age at diagnosis, extensive anatomical involvement, and the presence of fistula or strictures. In patients without risk factors or rapid progression, regular review with early escalation of therapy in cases with evidence of active disease is employed.

In an epidemiological study, it was found that a high proportion of IBD patients (95.5% in UC and 88.9% in CD) in Hong Kong were receiving 5-aminosalicylate acid (5-ASA) (1). Significantly more patients with CD than with UC had ever used corticosteroids (73.3% versus 50.5%; $P < 0.001$), immunosuppressants (73.7% versus 23.9%; $P < 0.001$), or anti-tumour necrosis factor agents (15.3% versus 1.6%; $P < 0.001$) (1). There are special considerations in using these medications in Hong Kong.

Firstly, a certain proportion of patients have hypermethylation skewed metabolism of azathioprine which is associated with impairment of liver function. This side effect has been shown to be managed successfully by the addition of allopurinol and reducing azathioprine dose by 25-33% (10). When this strategy is employed in Hong Kong where most of the population is Han Chinese, special attention should be given to the risk of severe mucocutaneous reactions (e.g. Steven Johnson Syndrome / Toxic Epidermal Necrolysis Syndrome) of allopurinol. HLA-B*58:01 allele is strongly associated with these mucocutaneous complications of allopurinol and is most commonly found in Korean, Han Chinese, or Thai (11). Patients should be warned about this side effect and allopurinol should not be used in patients tested positive with HLA-B*5801. Furthermore, several studies have shown that Asians with IBD had a specific genetic mutation (NUDT15 polymorphisms) that alter thiopurine metabolism and predisposes patients to bone marrow suppression (12).

Secondly, there are financial constraints in the use of biologics. In Hong Kong, the public health care system mostly supports the use of infliximab and adalimumab for CD with pre-defined indications. However new biologics including anti-integrin inhibitors are not reimbursed by the health-care system. In mainland China, patients have to pay for

biologics, and the cost is approximately US \$15,000 per patient per year .

Thirdly, the use of biologics is associated with reactivation of infections, in particular, hepatitis B and latent TB infection. In Hong Kong, 5.7 % of the IBD patients have chronic hepatitis B infection (13). HBsAg status should be checked in all patients with IBD. Pre-emptive use of antiviral agents is employed in all chronic hepatitis B patients who are receiving biologics therapy to prevent hepatitis B reactivation. Latent tuberculosis is also prevalent in Hong Kong and is screened in all patients before commencement of anti-TNF therapy by history taking, chest X-ray, tuberculin skin test and IGRA. 9-month course of single agent isoniazid prophylaxis will be given to patients screened positive for latent TB.

Conclusion

There is an increasing incidence of IBD in Hong Kong and China and the disease is as severe, if not more severe, than those in the West. There are unique challenges in the management of IBD in this part of the world, including the wide range of differential diagnosis and special considerations necessary in the use of IBD medications.

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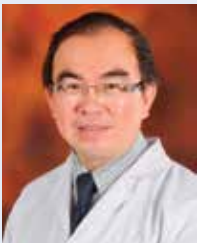
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Diagnosis and Management of Inflammatory Bowel Disease (IBD) in Southeast Asia



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Introduction

Southeast Asia (SEA) refers to a large region within Asia that encompasses countries with diverse ethnic populations and sociocultural backgrounds. Countries that fall within this region are Vietnam, Laos, Cambodia, Thailand, Myanmar, Malaysia, Indonesia, Singapore, Philippines, Brunei and Timor Leste. As can be seen from this list, SEA nations are of varying national affluence and industrialization status; these are factors that significantly impact access to healthcare in general. This translates to variations in the availability of routine vs specialized modalities in working-up a patient suspected to have IBD. Additionally, once diagnosed, managing these patients may also represent a challenge in view of limited access to newer therapeutic options.

Epidemiology of IBD within SEA

The incidence and prevalence of IBD within SEA varies widely from one country to another. In developed countries, the use of clinical registries as an integral part of the

health system ensures that patient information is captured and relevant statistical data is obtained. Unfortunately, this is not the case for many SEA nations. There are also the issues of properly defining catchment areas as well as having a standardized criteria for the diagnosis of IBD. IBD cases which are reported would most likely come from hospital-based data in larger cities, which may not accurately reflect accurate incidence and prevalence rates for the whole country. Patients too, may opt for alternative medical practices; gender and cultural norms would also affect healthcare-seeking behavior. These issues combined further illustrate the challenges faced in obtaining and reporting SEA IBD epidemiological information.

Nevertheless, despite these limitations it has been shown that the incidence and prevalence of IBD in the SEA region are on the rise; mirroring what is seen in the Asian continent generally. In comparison with the number of new IBD cases in Western countries which is thought to have plateaued, the incidence of new IBD patients within SEA member countries have been shown to be rapidly increasing in line with the pace of modernization. To a certain degree the rise in incidence may be attributed to an increased awareness regarding IBD, leading to a higher rate of new diagnoses being made. However, this would fully not explain the rapid rise in the number of new cases of IBD being diagnosed year after year.

The ACCESS paper in 2013 provided some valuable insight into the epidemiology of IBD within the Asia Pacific region. Several SEA nations participated in this study; namely Thailand, Malaysia, Singapore and Indonesia. It was shown that the age-standardized incidence of IBD for Thailand (Bangkok) was 0.58, Thailand (Chiangmai) was 0.54, Malaysia 1.01, Singapore 0.97 and Indonesia 0.83 (per 100,000 persons respectively). The ACCESS study also included Australian data, which showed an age-standardized incidence of 24.54/100,000 persons; much higher than the rates seen within the SEA countries that took part in the study (1).

Within the SEA region, there are more cases of ulcerative colitis (UC) as compared to those with Crohn's disease (CD). This contrasts with Western countries, where the gap between numbers of UC and CD patients is smaller. Rates of IBD also varies from one ethnic group to another. For example, in the multi-ethnic countries of Malaysia and Singapore, the incidence of UC is higher amongst ethnic In-

Diagnosis and Management of Inflammatory Bowel Disease (IBD) in Southeast Asia, continued.

dians than the Chinese or Malays. Conversely, Malays from these countries have less CD as compared to other ethnic groups (2, 3).

Diagnosis

As mentioned earlier, an increased awareness regarding the features of IBD has helped to contribute to better pickup rates. Nevertheless, before a diagnosis of IBD could be made it is important that possible differential causes be ruled out first. Common alternative diagnoses that may mimic the colonic lesions of IBD include infectious causes such as *Clostridium difficile*, enterotoxigenic *Escherichia coli*, *Mycobacterium tuberculosis* or *Entamoeba histolytica*. Examples of non-infectious causes that may also be mistaken as IBD include ischaemic colitis, non-steroidal anti-inflammatory drug use and Behçet's disease (4).

Whilst most infectious causes are self-limiting and tend to be identified after a short duration, the issue of differentiating gastrointestinal tuberculosis (TB) from IBD (especially CD) remains a major problem within SEA. TB is endemic in many SEA countries and must be considered as a differential cause for those that present with signs and symptoms suggestive of IBD.

As a start, a careful history must be taken to exclude other potential causes with a focus on determining prior contact with TB patients. History-wise, post-infectious irritable bowel syndrome may be mistaken as symptoms of IBD. Nevertheless, in endemic areas the patient may not even be aware of TB exposure and thus a high index of suspicion

for TB must be maintained. This is followed by a physical examination for signs suggestive of IBD but at the same time being on the lookout for other alternative diagnoses.

Subsequently, the patient will need to undergo further investigations to confirm a diagnosis of IBD.

Blood investigations

Apart from markers of inflammation (e.g., leucocyte count, erythrocyte sedimentation rate, C-reactive protein), serological markers may also be used to assist in the diagnosis of IBD. Whilst anti-*Saccharomyces cerevisiae* antibody (ASCA) and atypical perinuclear anti-neutrophil antibody (pANCA) testing are typically used to assist in diagnosing IBD, several other serological tests, e.g., anti-chitobioside antibody (ACCA), anti-laminaribioside antibody (ALCA) and anti-mannobioside antibody (AMCA), have also been suggested as additional tests to confirm a diagnosis of IBD. The utility of such tests within SEA however, may be limited. A comparison of these tests between Hong Kong Asian vs Australian Caucasian IBD patients showed differing serologic responses (5). Extrapolation of these results to a wider SEA community would indicate that such testing would probably be of limited value. These tests would also not be readily available at many local SEA centers; for many it would be an expensive test to order as samples are couriered and processed internationally.

In TB endemic areas, interferon-gamma release assay (IGRA) testing is recommended to exclude latent TB. IGRA testing is especially important prior to commencing im-

Table 1. Abdominal CT features in distinguishing CD from intestinal TB

	Feature	Sensitivity (95% CI)	Specificity (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)
1.	Comb sign	82 (78-85)	81 (74-86)	3.6 (2.3-5.7)	0.2 (0.1-0.5)
2.	Skip lesions	86 (82-89)	74 (67-80)	3.2 (1.1-9.4)	0.2 (0.1-0.6)
3.	Asymmetric bowel wall thickening	41 (36-46)	90 (85-94)	3.5 (0.6-21.9)	0.7 (0.5-1.1)
4.	Fibrofatty proliferation	41 (35-46)	89 (83-93)	3.1 (1.6-5.7)	0.7 (0.6-0.8)
5.	Long segment involvement	56 (47-66)	77 (65-87)	3.1 (0.9-9.6)	0.5 (0.4-0.7)
6.	Left colonic involvement	26 (20-32)	95 (88-98)	4.7 (1.9-11.6)	0.8 (0.7-0.9)
7.	Mural stratification	61 (55-66)	60 (52-67)	1.6 (0.7-4.1)	0.8 (0.5-1.1)

LR, likelihood ratio

Adapted from Kedia et al, 2017

Diagnosis and Management of Inflammatory Bowel Disease (IBD) in Southeast Asia, continued.

munosuppressive and immunomodulatory therapy which carries a high risk of latent TB reactivation (6, 7).

Radiological modalities

In many SEA nations, access to radiological modalities, e.g., computed tomography (CT) or magnetic resonance imaging (MRI), may be limited. Such modalities may only be accessible within larger cities – leaving those from rural areas without much choice with regards to radiological investigations to assist in making a diagnosis of IBD. Specialized radiological procedures such as CT or MRI colonoscopy, or even CT enterography/enteroclysis may not be available thus leaving clinicians with little options to assist in diagnosing (and managing) patients with IBD. Even when available, the cost of having such investigations may be prohibitive, thus limiting the use of such modalities. In such cases, the use of barium meal follow-through or barium enema studies may help in diagnosing IBD. Having said this, abdominal CT is a valuable tool to assist in differentiating intestinal TB from CD. Table 1 summarizes specific features seen on CT that may assist in differentiating between these two entities (8).

Nevertheless, as gut TB may also mimic the signs and symptoms of IBD, at the very least a chest radiograph

should be taken to rule out the presence of pulmonary tuberculosis. This is also important as subsequent immunosuppressive treatment may lead to worsening of pre-existing TB, which could be catastrophic for the patient.

Endoscopic evaluation

Gastrointestinal endoscopy remains the cornerstone of diagnosing IBD as it allows for visualization of mucosal lesions, as well as allowing for histopathological tissue samples to be obtained. Again, there may be a limited number of centers that offer this service, and even then, prolonged waiting times could lead to delays in diagnosing and managing IBD.

The mucosal lesions seen during ileo-colonoscopy in patients with IBD (especially Crohn's disease) may be indistinguishable from that of intestinal TB. However, it has been suggested that several endoscopic features may assist in differentiating the ileo-caecal lesions of CD as compared to those of intestinal TB; an involvement of less than four segments of the colon, a patulous ileo-caecal valve, transverse ulcers, and a greater amount of scarring all point to a preferred diagnosis of intestinal TB (9).

Table 2. Biologic therapies available commercially in SEA for the treatment of IBD in adult patients

	Name	Indication(s)	Antibody type	Mode of action	Administration	Dosing intervals
1.	Infliximab	Crohn's disease and Ulcerative colitis	Chimeric monoclonal antibody	Anti-tumour necrosis factor	Intravenous infusion	Induction: Week 0, 2 and 6 Maintenance: every 8 weeks
2.	Adalimumab	Crohn's disease and Ulcerative colitis	Fully humanised monoclonal antibody	Anti-tumour necrosis factor	Subcutaneous injection	Induction: Week 0 and 2 Maintenance: every 2 weeks
3.	Golimumab	Ulcerative colitis	Fully humanised monoclonal antibody	Anti-tumour necrosis factor	Subcutaneous injection	Induction: Week 0 and 2 Maintenance: every 4 weeks
4.	Vedolizumab	Crohn's disease and Ulcerative colitis	Fully humanised monoclonal antibody	Anti-α4β7 integrin	Intravenous infusion	Induction: Week 0, 2 and 6 Maintenance: every 8 weeks

Management of IBD in a Southeast Asian context

Consensus statements on the management of CD and UC have been released for the Asia-Pacific region (6, 7, 10). Generally, clinicians in SEA countries follow these statements to assist them in the optimal management of patients with IBD. These guidelines summarize the available evidence and provide recommendations as to the use of topical therapies, intravenous and oral corticosteroids, immunomodulators (thiopurines and calcineurin inhibitors especially) as well as the appropriate use of biologics and the role of surgical intervention. Apart from the Asia-Pacific consensus statements, clinicians in Malaysia also have access to a treatment algorithm which incorporates widely accepted IBD management strategies that have been customized according to locally-available treatment modalities (11).

Due to financial constraints, it is expected that conventional medications would remain the mainstay of treatment for patients with IBD. However, biologic therapy is recommended in patients that have indicators of poor disease outcomes (e.g., younger age, fistulizing disease, multiple relapses) or in those that have moderate to severe IBD (Table 2). It is a recognized fact that IBD treatment is costly; this is even more so when biologics are needed. Unfortunately, not many SEA countries offer public medical insurance to offset the high costs of biologic use. Singapore for example, has a high public health insurance coverage rate; this is low in Malaysia (12).

As highlighted previously, the use of immunosuppressive, immunomodulator and/or biologic therapy carries a significant risk of concomitant infection, of which tuberculosis is a major concern. A negative screening prior to initiation of biologic therapy does not eliminate the possibility of the patient having TB later (13). Thus, it has been suggested that gut-specific therapies (anti-integrins) or even biologics that target the IL12/23 pathway should be preferred over initiation with anti-tumor necrosis alpha biologics as these therapies have been associated with low risk of TB infection (14).

At the same time, it must be kept in mind that there is a high prevalence of Hepatitis B virus (HBV) infection within

SEA nations. Thus, it is important to screen patients with IBD for the presence of HBV prior to commencing immunosuppressive, immunomodulator and/or biologic therapies; those with a positive screening result will need to have prophylactic antiviral therapy to prevent HBV flares during this period.

Conclusion

Southeast Asia is a large region that encompasses many countries with diverse cultural, ethnic and socioeconomic backgrounds. Although the incidence and prevalence of IBD in this region is low as compared to Western countries, rates are increasing which may be linked to lifestyle, dietary and environmental changes. It is important that a diagnosis of IBD be made early as to prevent further disease-related complications, however, care must be taken to exclude the presence of tuberculosis which may mimic IBD. Prior to initiating therapy, one must make sure that patients are screened for HBV apart from other communicable diseases; and during therapy, patients will need to be constantly monitored for tuberculosis too as these infections are endemic within the SEA region.

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Inflammatory Bowel Disease (IBD) in Japan – Is it similar to or different from Western IBD?

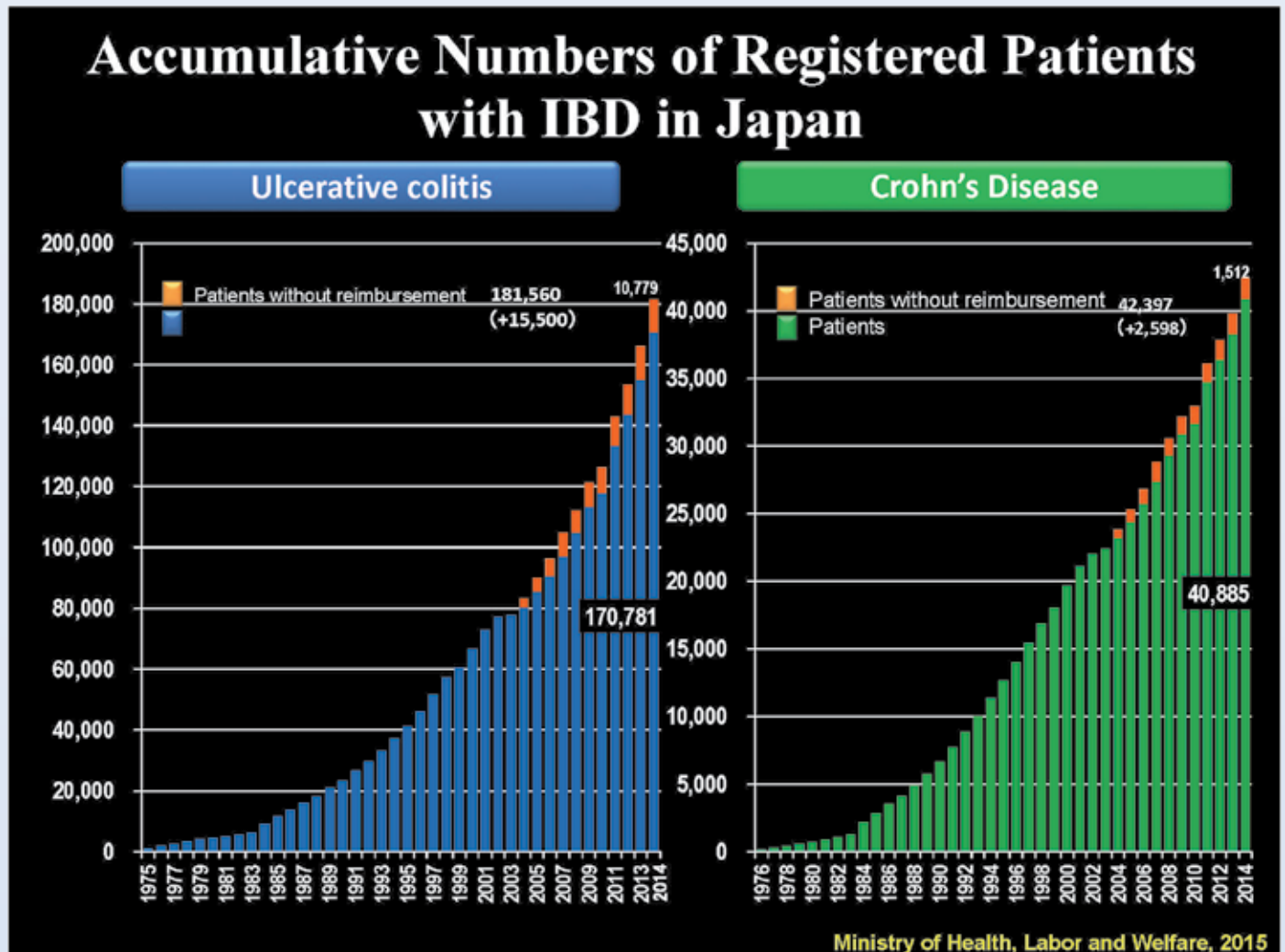


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on Intractable Gastrointestinal Inflammatory Disorders” supported by the Ministry of Health, Labour and Welfare (MHLW). When the Research Group was launched, little was known about the causes and clinical characteristics of these diseases, and appropriate research methods were also insufficient. However, over the course of 40 years since then, there has been a rapid increase in the number of basic research and epidemiological studies conducted to identify the clinical characteristics of these diseases, establish medical guidelines, and develop new therapies, which led to major changes in the current situation.

Research of inflammatory bowel disease (IBD) in Japan began in 1973 with the establishment of “Research Group

Figure 1.



Inflammatory Bowel Disease (IBD) in Japan – Is it similar to or different from Western IBD?
continued.

Figure 2.

Clinical guidelines for the management of Ulcerative Colitis (2016)				
Remission Induction therapy				
	Mild	Moderate	Severe	Fulminant colitis
Extensive colitis and left-sided colitis	Oral formulations: 5-ASA Enemas: 5-ASA, Steroid ※If the inflammation is severe in moderate cases or there is no improvement by the above therapy, oral administration of prednisolone should be given. ※If there is no improvement, therapy for severe and steroid refractory colitis should be given. ※ PENTASA suppositories are effective for rectal inflammation		Prednisolone intravenous infusion ※Combination therapy with the following medicines should be given according to symptoms: Oral formulations: 5-ASA Enemas: 5-ASA, Steroid ※If there is no improvement, therapy for steroid refractory colitis should be given. ※Depending on symptoms, surgery should be considered.	Emergency surgery should be considered. ※If possible, the following therapy may be applied under collaboration with surgeons: •High-dose steroid intravenous therapy •Cytapheresis • Oral tacrolimus • Cyclosporine continuous intravenous therapy* ※If there is no improvement with the above therapy, surgery is recommended.
Proctitis	Oral formulations: 5-ASA Suppositories: 5-ASA, Steroid Enemas: 5-ASA, Steroid ※Easy use of systemic steroid should be avoided.			
Intractable patients	Steroid dependent colitis		Steroid refractory colitis	
	Immunomodulators: azathioprine, 6-MP* ※If there is no improvement, Cytapheresis, Oral tacrolimus, Intravenous infliximab, or Subcutaneous adalimumab could be considered.		Moderate: Cytapheresis, Oral tacrolimus, Intravenous infliximab, Subcutaneous adalimumab Severe: Cytapheresis, Oral tacrolimus, Intravenous infliximab, Subcutaneous adalimumab, Cyclosporine continuous infusion therapy* ※Combination therapy with azathioprine /6-MP* could be considered. ※If there is no improvement, surgery should be considered.	
Remission maintenance therapy				
	Non-refractory		Refractory	
	5-ASA formulations (oral, enema, suppositories)		5-ASA formulations (oral, enema, suppositories) Immunomodulators (azathioprine, 6-MP), Intravenous infliximab, Subcutaneous adalimumab**	

*: not covered by insurance. **: apply when induction of remission is achieved by infliximab

Epidemiology

The current number of patients in Japan continues to increase, with at least 180,000 patients suffering from ulcerative colitis (UC) and 40,000 suffering from Crohn's disease (CD). (Fig. 1).

Incidence and prevalence

According to a survey conducted by MHLW in 2014, the incidence was 12.2 in UC and 2.0 in CD per 100,000 people and the prevalence was 133.2 in UC and 31.9 in CD per 100,000 people. Although similar increases in the number

of patients are being observed in other Asian countries, the prevalence remains lower than that in Western countries.

Gender differences and age at onset

The age at onset is similar to western countries in both disease, but gender difference is seen in CD. The male-to-female ratio is 2:1; that is also observed in other Asian countries including Korea and China, in contrast with no gender-based differences observed in Western countries.

Inflammatory Bowel Disease (IBD) in Japan – Is it similar to or different from Western IBD?
continued.

Figure 3.

Clinical Guidelines for the Management of Crohn's Disease (2016)			
Treatment in the active period (Combined treatment with nutritional therapy and/or medication could be applied according to symptoms and patient's tolerance)			
Mild to moderate	Moderate to severe	Severe (severely active or advanced complications)	
<p>Medication</p> <ul style="list-style-type: none"> • Pentasa® sachet/tablet • Salazopyrin® tablet (colonic lesion) <p>Nutritional therapy (enteral nutritional therapy) When patients tolerate, this therapy is applied.</p> <ul style="list-style-type: none"> • Elemental diet (Elental®) • Digestible nutrients (Twinline®) <p>※ Semi-digestion nutrition agent can be applied if low tolerance.</p> <p>※ If there is no improvement, therapy for moderate to severe Crohn's disease should be considered.</p>	<p>Medication</p> <ul style="list-style-type: none"> • Oral steroids (prednisolone) • Antimicrobials (metronidazole, ciprofloxacin) <p>※ Intractable cases for steroid tapering/weaning: azathioprine, 6-MP</p> <p>※ Non-responders to steroids and/or nutritional therapy: infliximab, adalimumab</p> <p>Nutritional therapy (enteral nutritional therapy)</p> <ul style="list-style-type: none"> • Elemental diet (Elental®) • Digestible nutrients (Twinline®) <p>※ Semi-digestion nutrition agent can be applied if low tolerance.</p> <p>Cytapheresis</p> <ul style="list-style-type: none"> • Granulocytapheresis (Adacolumn®) <p>※ Apply to non-responders/intolerance with symptoms from colonic lesions to conventional therapy.</p>	<p>After considering surgeries, the following medication should be given:</p> <p>Medication</p> <ul style="list-style-type: none"> • Steroids (oral or intravenous) • infliximab, adalimumab (refractory to conventional therapy) <p>Nutritional therapy</p> <ul style="list-style-type: none"> • Total parenteral nutrition should be given under fasting <p>※ Switch to enteral nutrition therapy when improved</p> <p>※ Infliximab and adalimumab can be administered patients without obstructions and abscesses.</p>	
		Stenosis therapy	Post-operative relapse prevention
<p>Medication</p> <ul style="list-style-type: none"> • 5-ASA: Pentasa® sachet/tablet, Salazopyrin® tablet (colonic lesions) • azathioprine, 6-MP • Infliximab, Adalimumab (Remission achieved patients with these biologics) <p>Home parenteral nutritional therapy</p> <ul style="list-style-type: none"> • Elental®, Twinline® <p>※ Semi-digestion nutrition agent can be applied if low tolerance.</p> <p>※ This therapy should be considered for patients with difficulty in nutrition management such as short-bowel syndrome patients.</p>	<p>Surgical treatment should be considered, first. Drainage and seton treatment</p> <p>Medical treatment:</p> <ul style="list-style-type: none"> • Anal fistulas and perianal abscesses: metronidazole*, antimicrobials, antibiotics, infliximab • Anal fissures and perianal ulcers: same medication as intestinal lesions • Anal stenosis: transanal dilation 	<p>[Stenosis] Surgical treatment should be considered, first.</p> <ul style="list-style-type: none"> • Inflammation should be reduced with medication, then endoscopic balloon dilation can be applied after confirming healing or shrinking of ulcers. <p>[Fistula] Surgical treatment should be considered, first.</p> <ul style="list-style-type: none"> • Medication (external fistula): infliximab, adalimumab, azathioprine 	<p>Apply same treatment as remission maintenance therapy:</p> <p>Medication</p> <ul style="list-style-type: none"> • 5-ASA: Pentasa® sachet/tablet, Salazopyrin® tablet (colonic lesions) • Azathioprine, 6-MP* <p>Nutrition therapy</p> <ul style="list-style-type: none"> • Enteral nutritional therapy <p>※ Combination with medication can be applied.</p> <p>*: not covered by insurance</p>

Mortality rate

According to a demographic survey conducted in 2011, 129 people died due to UC (81 males and 15 females). Using these data, the age-adjusted mortality rate was 0.046 (males: 0.068 and females: 0.029). The number of deaths attributed to CD was 43 (28 males and 15 females) and the age-adjusted mortality rate was calculated at 0.026 (males: 0.037 and females: 0.016).

Carcinogenicity

Cancer is a serious complication associated with long-term UC. In Japan, the frequency of colon cancer in patients with UC is 2.6% (123 in 4,756); the rate is under 2% up to 10 years following onset, approximately 5% after 10 years, and over 10% after 21 years, which is similar to Western countries. For cancer surveillance, we demonstrated that targeted and random biopsies detect similar proportions of neoplasias in a randomized controlled trial. Colorectal cancer as a complication of CD is not well surveyed, but the tendency is the same as in western countries. It is com-

*Inflammatory Bowel Disease (IBD) in Japan – Is it similar to or different from Western IBD?
continued.*

monly seen in young patients with long disease duration, characterized by a high percentage of mucinous carcinomas. Other reported complications include small intestinal cancer and anal fistula cancer.

Hereditary predisposition

The fact that IBD commonly occurs among members of the same family has been reported in both Western countries and Japan. The closer the blood relationship, the higher the rate of onset, suggests that shared environmental factors play a role in addition to hereditary predisposition.

Hereditary predisposition in Asia including Japan, is different from that in western countries. In 2001, NOD2, was identified as a Crohn's disease susceptible gene by linkage analysis. However, since our first report on the absence of NOD2 in the Japanese population,² almost all genes abnormalities found in western population, have reported no or little association with Asian populations, except for TNFSF15 and FcγRII.³ These findings indicate that the genetic risk of IBD is quite different between western IBD and Japanese IBD population.

Environmental factors

In UC, one of the main environmental factors is smoking, which is thought to lower the risk of onset and severity of the disease as well as in western persons. Appendectomy is also reported to be protective.⁴ In addition, the Research Group has suggested that the excessive intake of sugar and processed meats, and the use of oral contraceptives are risk factors. However, the mechanism as to how they would affect risk remain unknown, and there is no consensus regarding the influence of each of these risk factors.

An important environmental factor related to CD is smoking. Smoking is reported as a risk factor for the onset and relapse of CD. Although various factors may be related to the pathogenesis of CD, there is no clear consensus regarding other environmental factors similar to UC.

Diagnosis

Diagnostic procedures are almost the same as in western countries. It is necessary to take a detailed history of the patient and perform bacteriological examinations, especially mycobacterium tuberculosis tests in Asia to rule out intestinal tuberculosis. Next, ileocolonoscopy should be performed to obtain characteristic endoscopic findings.

Patients with infectious enteritis often exhibit the similar initial symptoms and endoscopic findings as those with UC.

In Japan, diagnostic criteria for CD are based on the macroscopic and microscopic identification of characteristic gastrointestinal lesions. As it is necessary to differentiate the disease from other inflammatory intestinal diseases such as intestinal Behcet's disease and intestinal tuberculosis, its diagnosis should be made by excluding infections through bacteriological examination and tuberculosis testing in combination with an endoscopic examination.

Endoscopic examination

1. Ileocolonoscopy

Ileocolonoscopy is necessary to make a diagnosis for UC. In Japan, ileocolonoscopy is usually used for diagnosis and monitoring, more so than just endoscopic examination of the rectum or sigmoid colon.

Lesions associated with CD are mainly found in the small intestine particularly in the terminal ileum. Thus, ileocolonoscopy is the most important diagnostic examination for patients with CD.

2. Balloon-assisted enteroscopy

In many patients with CD, lesions occur in the small intestine; therefore, they are often found at sites that cannot be accessed by ileocolonoscopy. Balloon-assisted enteroscopy allows the direct observation of the mucosa of the small intestinal lesions that would otherwise be impossible with other modalities and also enables physicians to obtain biopsy samples of mucosal tissue. Other advantages of balloon-assisted enteroscopy include endoscopic hemostasis for bleeding ulcers and balloon dilatation for intestinal stenosis. Therefore, balloon-assisted enteroscopy is often used in Japan.

Histopathological examination is performed at every endoscopic examination. The characteristic histological findings in UC and CD are completely the same as in western countries.

3. Small intestinal capsule endoscopy

Small intestinal capsule endoscopy has been reported to be effective in patients with CD. An advantage of this examination is its non-invasiveness as a screening method of the small intestine. However, attention is required as there is a risk of capsule retention due to stenosis in the small

Inflammatory Bowel Disease (IBD) in Japan – Is it similar to or different from Western IBD? continued.

intestine, which is commonly associated in patients with CD. So, the patency capsule should be performed first to evaluate the stenosis before capsule endoscopy examination is undertaken.

Small bowel barium through study

Small-bowel barium follow through studies are still common in Japan. In patients with CD having lesions in the small intestine, small-bowel barium studies allow the observation of the distribution of lesions and provide plenty of information in relation to stenosis and dilation of the small intestinal tract, fistula formation, and adhesions.

Computed tomography/magnetic resonance imaging enteroclysis/enterography

Imaging using computed tomography or magnetic resonance imaging (MRI) with an oral contrast medium to dilate the gut lumen allows small intestinal lesions to be observed with a high diagnostic accuracy. In patients who require repeated examination of small intestine, MRI—which does not expose patients to radiation is useful especially in young patients. Thus, MRI has become more popular in Asia as well as in western countries.

Treatment

Medical treatment in UC

The treatment guidelines for UC released in 2016 by the MHLW Research Group are shown in Table 1. In recent years, novel treatment options have been developed that have made it possible to avoid surgery for more refractory patients.

1. Induction therapy

In Japan, salazosulfapyridine (SASP) and mesalazine are the forms of 5-ASA covered by the Japanese insurance. MMX-5ASA was approved at the end of 2016, in addition to Pentasa and Asacol.

In patients with mild-to-moderate UC in which 5-ASA is insufficiently effective, oral corticosteroid can be added to the treatment regimen. Oral prednisolone is used at a dose of approximately 30–40 mg/day, and when necessary, it can be administered intravenously. As an alternative therapy for patients who are refractory to corticosteroids, leukocytapheresis therapy is commonly applied in Japan for the removal of leukocytes (granulocytes, lymphocytes and monocytes). This therapy has fewer serious adverse

effects than corticosteroid and immunosuppressants with similar therapeutic effect to corticosteroids. However, this therapy has not been proved to be effective overseas.

In severe and fulminant cases of UC, patients should be hospitalized and placed on a regimen of either oral or intravenous prednisolone. In patients where the corticosteroids are ineffective, general care should be initiated with the possibility of switching to calcineurin inhibitors, anti-TNF-alpha antibodies or surgery.

Calcineurin inhibitors used in Japan are tacrolimus and cyclosporine. Although they have also a relatively high remission induction rate, relapse after remission induction is common. In Japan, the anti-TNF-alpha antibodies available for use in patients with UC include infliximab and adalimumab. Golimumab has come on the market this year. Among adverse drug effects, particular attention is required to prevent activation of tuberculosis or hepatitis B in Asia. In patients who are refractory to these treatments with a poor general condition, colectomy is the treatment of choice. Anti-a4b7 antibody will be available in Japan next year.

2. Maintenance therapy

It is important to use maintenance therapy for prevention of relapse during the remission phase of UC. The basic medication used for remission maintenance is 5-ASA, although adherence is extremely important. In patients who have difficulty in discontinuing corticosteroids, such as those who relapse upon dose reduction, the administration of the immunomodulators, such as 6-mercaptopurine (6-MP) or azathioprine (AZA) is recommended. Recent reports revealed that NUDT15 gene abnormalities are associated with adverse effects of leukopenia and alopecia in Asian people.⁵

Medical treatment in CD

The treatment guidelines indicated by the MHLW Research Group in 2016 are shown in Table 2. Medical treatment mainly consists of a combination of nutritional, drug, and endoscopic therapies.

1. Induction therapy

Patients with mild-to-moderate CD are treated using a regimen of 5-ASA and nutritional therapy. However, efficacy of 5-ASA is less for CD than for UC, and even questionable. In Japan, the nutritional therapy used to be in a main stream as primary treatments for CD, although its mechanism of action

*Inflammatory Bowel Disease (IBD) in Japan – Is it similar to or different from Western IBD?
continued.*

has not been well elucidated. In Western countries, nutritional therapy is not widely used for adult patients because adherence is generally low. However, nutritional therapy can be highly effective for small intestinal lesions, and it is recommended particularly in those with pediatric CD.

In patients with CD who are difficult to be controlled with 5-ASA and/or nutritional therapy, oral corticosteroid is considered. Oral corticosteroids include prednisolone and budesonide, which was recently approved in Japan. Since corticosteroids are not effective for remission maintenance, more recently, such patients are increasingly early being started on early introduction of anti-TNF-alpha antibodies. The recent emergence of anti-TNF-alpha antibodies has led to the possibility of changing the natural course of CD. Anti-TNF-alpha antibodies not only rapidly induce clinical remission but also are effective in healing intestinal mucosal lesions. Thus, the timing of the use of these drugs is crucial. In addition to anti-TNF-alpha antibodies, anti-IL12/23 antibody has become available in Japan this year.

2. Maintenance therapy

The effectiveness of 5-ASA and corticosteroids as remission maintenance therapy has not been demonstrated. Nutritional therapy is effective in maintaining remission and has also been reported to reduce the rate of repeated surgery when conducted as postoperative therapy. In patients in whom 5-ASA and nutritional therapy are insufficiently effective and in whom discontinuing steroids is difficult, the immunomodulators (6-MP or AZA) are used for the maintenance. When remission is induced by anti-TNF-alpha antibodies, they are used also for the maintenance of remission.

3. Treatment of anal lesions

The treatment of anal lesions includes the examination to determine the necessity of surgical intervention of perianal abscesses and drainage by setons. Medical treatment includes the administration of immunomodulators and/or anti-TNF-alpha antibodies.

4. Treatment of stenosis and fistulae

In patients complicated with stenosis and fistulae, the need for surgery should be first investigated. Medical treatments include balloon dilatation of stenoses by ileocoloscopy or balloon-assisted enteroscopy. Surgery is the first-line therapy for internal fistulae especially with infection, but

depending on the clinical condition, anti-TNF-alpha antibodies and immunomodulators may be administered.

There are some differences in epidemiology, diagnosis and therapy of IBD between western countries and Asia, especially Japan, but, these differences have become smaller.

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Inflammatory Bowel Disease (IBD) biomarkers and their use in clinical practice



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KEY TERMS

CLINICAL REMISSION:

The patient reports that they are asymptomatic

ENDOSCOPIC REMISSION:

No active disease found on endoscopy

Mucosal healing has become the new therapeutic goal

DEEP REMISSION:

Clinical and endoscopic remission

Introduction

The current gold standard technique for assessing inflammatory bowel disease (IBD) disease activity is ileocolonoscopy. However, this is invasive, expensive, time-consuming, and not without risk. Unfortunately, symptoms and clinical signs do not always correlate well with intestinal inflammation, therefore developing biomarkers to use alongside clinical assessment may assist in evaluating intestinal inflammation non-invasively.

In clinical practice, clinicians may use informal or formal (e.g. the Clinical Colitis Activity Index and the Crohn's Disease Activity Index) measures of clinical disease activity. Biomarkers are able to augment the evaluation of IBD activity if they can accurately reflect the presence and severity of intestinal inflammation. As almost all therapies for IBD work through the reduction of inflammation, accurate

clinical assessment coupled with validated biomarkers offer the promise of reducing the burden of endoscopy on patients and healthcare systems while ensuring that the right patient gets the right treatment at the right time. Timely and appropriate treatment may lead to a reduction in disease complications including irreversible bowel damage, hospitalisation and surgery.

During periods of apparent clinical remission, histological changes of inflammation can often be found in the colon. A non-invasive way of detecting subclinical inflammation would allow appropriate and individualised treatment regimes.

In this chapter, we will discuss the use of biomarkers available to clinicians in everyday practice and their correlation to IBD activity.

Routine blood tests

While there are a plethora of new biomarkers that promise improved sensitivity and specificity, the importance of routine blood tests should not be forgotten.

Full blood count

Components of the full blood count can be useful indicators of inflammation and IBD activity. The white cell count and mean platelet count may be increased in patients with active compared with inactive IBD, and can correlate with the degree of intestinal inflammation.

Anaemia is common and multifactorial in inflammatory bowel disease with causes including:

- Bleeding
- Nutritional deficiencies (inflammation or post-surgical)
 - o Iron
 - o Vitamin B12
 - o Folic Acid
- Chronic disease state (suppression of erythropoietin production and alteration of iron metabolism caused by inflammatory cytokines)

Biochemistry

Albumin

Most cases of hypoalbuminaemia are caused by acute or chronic inflammatory processes. Other causes include

Inflammatory Bowel Disease (IBD) biomarkers and their use in clinical practice, continued.

the nephrotic syndrome, hepatic cirrhosis, heart failure, and malnutrition. Hypoalbuminaemia can be the result of the combined effects of inflammation and inadequate protein and caloric intake in patients with chronic disease, therefore nutritional assessment is vital.

Inflammatory markers

Of all laboratory assessments that have been studied for evaluation of disease activity in IBD, C-reactive protein (CRP) and faecal calprotectin (FC) are the most widely adapted in clinical practice.

CRP

CRP is an acute phase reactant, and is an objective marker of inflammation with several clinical uses in IBD management. It has been associated significantly with other biomarkers of inflammation including erythrocyte sedimentation rate (ESR), thrombocytosis, anaemia, and hypoalbuminemia. CRP is not specific for intestinal inflammation but does have modest correlation with clinical and endoscopic findings in inflammatory bowel disease.

Crohn's disease (CD) v Ulcerative colitis (UC)

CRP is reliably raised in cases of transmural intestinal inflammation but can be falsely low in cases of superficial mucosal inflammation alone. It therefore correlates well with disease activity in CD, but less well in UC. Some persons do not make CRP and hence, regardless of the inflammatory burden will not have an elevated CRP. There are no significant differences in CRP concentrations based on disease localisation of CD (ileitis, colitis, or ileocolitis)

Correlation with endoscopic inflammation

CRP elevations (>8 mg/L) are associated significantly with moderate to severe clinical activity. A large meta-analysis of 19 studies suggested a CRP cut-off of >5mg/L to indicate active endoscopic disease, with a sensitivity and specificity of 49% and 92%, respectively¹. However, CRP is not reliable in predicting endoscopic remission. CRP was falsely negative (< 3 mg/L) nearly twice as often as actual endoscopic remission in one study². Post-operative monitoring of CRP does not strongly correlate with CD activity.

Raised CRP concentrations (>5mg/L) correlate with an increased risk of:

- Clinical relapse
 - o Short and long term
 - o CRP may rise 4-6 months before clinical relapse
 - o Rapid normalization of CRP concentrations correlates with sustained long-term response to biological agents
- Hospitalisation
- Surgery
 - o CD patients with terminal ileitis are 6 times more likely to need future surgery if CRP concentrations at diagnosis are above 53 mg/L
 - o At 1 year, UC patients with a CRP concentration greater than 10 mg/L were 3 times more likely to require surgery in the next 4 years³

CRP SUMMARY

- Raised concentrations correlate with intestinal inflammation, especially for transmural Crohn's disease.
- CRP correlates with risk of relapse and need for future surgery.
- A normal result does not rule out intestinal inflammation in IBD patients.

ESR

ESR is the rate at which erythrocytes migrate through the plasma. Inevitably, ESR will depend on the plasma concentration, the number and size of red blood cells. Conditions such as anaemia, polycythaemia, and thalassemia affect ESR. Levels also increase with age.

Its long half-life and interference with other factors makes it less useful in clinical practice compared to CRP. ESR is inferior to CRP in differentiating between an inflammatory bowel process and IBS and has an inferior correlation with endoscopic disease activity in cases of confirmed IBD.

Inflammatory Bowel Disease (IBD) biomarkers and their use in clinical practice continued.

Faecal Calprotectin (FC)

FC is an inflammatory protein found in neutrophils, macrophages, and monocytes.

The presence of calprotectin in the faeces is directly proportional to neutrophil migration into the gastrointestinal tract during times of inflammation. Many gastrointestinal conditions can lead to elevations in FC concentrations including IBD, pouchitis, diverticulitis, malignancy, infections, nonsteroidal anti-inflammatory drug (NSAID) enteropathy, alcohol enteropathy, pancreatic insufficiency, coeliac disease, and microscopic colitis. Faecal calprotectin concentrations also rise with age.

For the assessment of mucosal inflammation, FC has consistently been shown to be superior to clinical indices and serum parameters such as CRP.

Crohn's disease V ulcerative colitis

In CD there is a significant correlation between FC and colonic and ileocolonic inflammation, with the day-to-day variability in the concentration of calprotectin in faecal samples being low. In isolated ileal disease the FC is often still positive, but has a weaker correlation with the degree of inflammation seen on endoscopy.

With UC, the variability of calprotectin concentrations in faeces varies widely. Giving a morning sample is suggested to avoid a false negative result. UC patients in clinical remission tend to have FC concentrations that positively correlate with endoscopic inflammation.

Correlation with endoscopic inflammation

FC has been used to monitor IBD patients during periods of clinically quiescent disease. A cut-off of 50mcg/g has been associated with mucosal healing in patients with IBD, but normal results do not always confirm endoscopic remission.

In several studies, the patients with UC or CD who relapsed were found to have consistently elevated FC levels prior to relapse. There was a significant increase in FC levels at 2, 4, and 6 months before endoscopic relapse. This suggests that the trend, rather than an isolated measurement, may be more valuable in predicting relapses.

FC has also been proven to be more accurate than CRP at reflecting CD recurrence after surgery.

Faecal Calprotectin summary

1. Diagnosis and management of IBD:
 - a. In the setting of undifferentiated diarrhoea in patients with no alarm symptoms, FC can be used to exclude inflammatory disease and could preclude the need for more invasive investigations.
 - b. In patients known to have IBD, FC can be used for monitoring of disease activity and can provide prognostic information.
2. FC is more specific for intestinal inflammation than CRP, and is more reliable at detecting post-operative CD recurrence.

Lactoferrin

Lactoferrin is a major component of the secondary granules of neutrophils and therefore its levels rise rapidly with inflammation. From the limited number of studies available, lactoferrin seems to mirror calprotectin in its ability to differentiate between inflammatory bowel conditions and irritable bowel syndrome (IBS). It can also be used to monitor response to IBD therapy and predict the risk of relapse. The ability to distinguish CD from UC based on a lactoferrin result has been theorised in some studies but is controversial.

Novel biomarkers

Volatile organic compounds

Investigations into the metabolomic profile of patients is an exciting new development in the diagnostic pathway of inflammatory bowel disease. The production of volatile organic compounds (VOC) reflects the gut fermentome metabolites, with various compounds identified from faecal, breath and urine samples. VOCs may be altered in certain disease states, and analysis of breath VOC profiles have been shown to distinguish IBD from controls, and have shown distinct individual patterns in CD and UC⁴.

The future of biomarkers

Biomarkers play an important role in helping clinicians identify the presence and severity of inflammation. However, recent studies such as CALM are demonstrating that biomarkers could be used as a therapeutic target, over and above clinical symptoms, leading to tighter disease control. Further work is needed to define the best biomarkers to use,

Inflammatory Bowel Disease (IBD) biomarkers and their use in clinical practice continued.

the frequency of using them and whether this strategy will lead to increased rates of endoscopic and deep remission.

Case studies

70 year old lady presents with 2 weeks of diarrhoea. WCC $14 \times 10^9/L$, platelets $540 \times 10^9/L$ (140–400), CRP 24mg/L, Faecal calprotectin $>500\text{mcg/g}$

- This lady has an acute inflammatory diarrhoea
- The calprotectin has provided limited discriminatory information over and above the WCC, CRP and platelet count
- She requires stool microbiology testing. If symptoms are persistent and stool microbiology testing is negative then colonoscopy should be considered.

26 year old female with 5 months of abdominal pain and loose bowel motions. Stool microbiology normal, normal haemoglobin, platelet count and albumin. CRP $<5\text{mg/L}$, Faecal calprotectin $<50\text{mcg/g}$

- There is no biochemical evidence of inflammation
- Possible IBS, but warrants clinical review

40 year old male. Ileocolonic CD on adalimumab. Increased abdominal pain and diarrhoea over the past 6 weeks. CRP $<5\text{mg/L}$, Faecal calprotectin 125mcg/g

- Minimal evidence of biochemical activity, but borderline calprotectin level
- Should rule out non-inflammatory causes of GI symptoms in patients with CD including IBS, small intestinal bacterial overgrowth, bile acid malabsorption, fibrotic stricture

54 year old female with ulcerative colitis in clinical remission for many years on 5-ASA alone. 4 week history of mild bloody diarrhoea. CRP $<5\text{mg/L}$, Faecal calprotectin 260mcg/g

- Clinically relapsing
- CRP and calprotectin can be falsely low in active UC

32 year old male. Diagnosed with ileal Crohn's disease aged 25. Currently on mesalazine and is asymptomatic. CRP 7mg/L. Faecal calprotectin 340–370mcg/g on 3 separate occasions over the past 6 months.

- Clinically stable
- Subclinical inflammation with a CRP of 7mg/L and raised calprotectin suggesting active disease
- Repeat colonoscopy with possible alteration of therapy should be considered

Comments

- In most cases, basic blood test markers of inflammation are helpful. If these are negative, faecal calprotectin may be useful to identify inflammation.
- In cases of known IBD in clinical remission, the results from biomarkers can identify "silent" Crohn's disease.

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WGO Checklist: Pre Biologics Use



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Biologics have been largely used by gastroenterologists worldwide to treat Inflammatory Bowel Disease (IBD). Prior to the use of biologics, it is important to consider the appropriate time to start biologic therapy and the implications for the patient. Make sure the use of the biologic therapy is appropriate, talk to the patient about the risks and benefits of the drug(s), and ensure that the patient is well informed.

Additional tips to consider prior to the start of biologic therapy:

1. Avoid giving biologics to patients with suspected infection. A draining fistula is not a contraindication for the use of biologics.
2. Discuss their effects on pregnancy or breastfeeding.
3. Make the appropriate biologic therapy choice together with the patient.
4. In the case of reintroducing a biologic, be aware of previous sensitivity.
5. In the case of anti-TNF, be careful of moderate to severe heart failure
6. Always exclude the risk of active or latent tuberculosis (TB).

If a patient is experiencing severe diarrhea, or diarrhea with fever and bleeding, clinicians should check whether the patient is infected with *Clostridium difficile* or cytomegalovirus (in patients already using corticosteroids or immunosuppressives). These infections could be driving symptoms in the absence of active IBD.

Pre-infusion screening at baseline (to complete prior to starting biologic therapy)

1. Tuberculosis

- Obtain patient's full TB History (check family history, travel history and profession history).

- Complete screening (Mantoux, skin test) or other TB test (Quantiferon gold or IGRA) if available locally
- Take chest x-ray.

2. Routine blood test, to evaluate

- HIV serology
- Hepatitis B and C serology
- VZV serology
- CBC BUN, Creatinine, liver enzymes, ESR and CRP, and Ferritin

3. Vaccinations

- Obtain the patient's full vaccination history (vaccination before the administration of biologics is recommended, when possible).

Recommendations for past and current vaccinations:

- No live vaccines in the last four weeks
- VZV (Varicella Zoster Vaccine) should be administered if not within the previous 5 years
- HPV (Human Papilloma Virus)
- Influenza (trivalent inactivated vaccine) once a year
- Pneumococcal polysaccharide vaccine should be given if not previously administered
- Hepatitis B vaccine in all HBV seronegative patients

Ideally, vaccinate non-immune patients prior to immuno-suppressive treatment dependent on the results of the examinations listed below. Examinations and vaccinations to perform:

- **Hepatitis A antibody (IgG)** – vaccinate if non-immune to hepatitis A
- **Anti-HBs AB** – vaccinate if insufficient antibody response
- **Anti-HBcAb and HBsAg** – the former indicates current or previous infection; the latter indicates current infection
- **Anti-pneumococcal antibody** – vaccinate if insufficient antibody response
- **Anti-Varicella Zoster Virus** – vaccinate if insufficient antibody response
- **HPV vaccine** in younger females

WGO Checklist: Pre Biologics Use, continued.

Also check the following:

- **TPMT assay** – should be used prior to initiating thiopurine depending on availability (not yet routinely available in Latin America)
- **Anti-HCV** – indicates current or previous infection
- **Recent cervical screen performed** – cervical neoplasia is a contra-indication to thiopurine use. Live vaccines are contraindicated during and up to 3 months after treatment with anti-TNF, and some inactive vaccines may be less effective and require further immunization.

Pre-biologic therapy check list

1. Request a Chest X-ray.
2. Request Interferon-gamma or skin test for Mycobacterium tuberculosis.

Frequently Asked Questions

1. What if the patient has evidence of hepatitis B infection?

- Patients should be treated for at least 6 months beyond the planned duration of anti-TNF. Lamivudine or Telbivudine can be used if the anticipated duration of treatment is ≤ 12 months and baseline serum HBV DNA is not detectable; otherwise use Tenofovir or Entecavir.

2. What if the patient has evidence of latent TB or TB infection?

- Treat latent TB for at least 3 weeks with Isoniazid before starting anti-TNF and continue Isoniazid for a total of 6-9 months. Anti-TNF should only be started in patients with overt TB once the disease has responded to therapies to which it is known to be sensitive.

Example of Pre-Biologic Therapy Checklist

Medical History	Y	N	Comments
Demyelinating disease in person or family, i.e. rst-degree relative (e.g. MS: optic neuritis)	Y	N	
Signs and symptoms of active TB Past H/O TB or close family member contact with active TB	Y	N	
H/O Hep B, Hep C, HIV	Y	N	
H/O allergies (e.g. latex, egg)	Y	N	
Past history of malignancy (except NMSC)	Y	N	
H/O cardiac failure	Y	N	
Contraception (if relevant, follow guidelines)	Y	N	
Immunosuppression in last 3 months	Y	N	

Vaccination and Screening	Y	N	Comments
H/O BCG vaccination	Y	N	
Recommend pre-treatment vaccinations	Y	N	
Influenza	Y	N	
Pneumococcal	Y	N	
Varicella zoster	Y	N	
Last cervical pap smear (if relevant)	Y	N	Date:

Clinical Examination	Comments
Height	
Weight	
Baseline BP	
Full skin examination	

By signing below, the patient acknowledges that the Doctor discussed the side effects of the biologic therapy with them. Side effects that were discussed may include but are not limited to risk of infection, malignancy, demyelination; and advised the patient on avoiding live vaccines 2 weeks before, during and 6 months after the biologic therapy.

Signature (consent of patient):

Date:



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WGO Checklist: Pre Biologics Use, continued.

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Crohn's disease and tuberculosis; clues to solving the diagnostic dilemma



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Highlights

With increasing prevalence of Crohn's disease (CD), distinguishing it from intestinal tuberculosis (ITB) is of utmost importance as misinterpretation may lead to incurable consequences. This chapter will concisely review the resemblance and dissimilarities between the two ailments, considering their clinical, endoscopic, radiological and histological physiognomies.

Introduction

Mycobacterium bovis (*M. bovis*) is notorious to cause primary intestinal tuberculosis (ITB), which spreads via unpasteurized milk. However, with socioeconomic development, this has now become rare. These days involvement of gastrointestinal tract (GIT) secondary to pulmonary tuberculosis is the main reason of ITB (1, 2).

Inflammatory Bowel Disease (IBD) is a disorder of undetermined etiology illustrated by chronic or relapsing immune activation leading to inflammation within the gastrointestinal tract (GIT). It encompasses Crohn's Disease (CD) and Ulcerative Colitis (UC), both share various clinical and epidemiologic features, signifying that the fundamental pathophysiologic basis is the same (3). Out of the two, CD shares puzzlingly similar clinical, endoscopic, and pathological appearances with ITB so much that misdiagnosis rate of CD and ITB is as high as 50-70% (1).

Epidemiology

Despite the declaration of TB as a global health problem by World Health Organization in 1993, still, the encumbrance of this disease is very high, infecting around one-third of the world's population (3). Around 9 million new cases were reported and 1.5 million deaths worldwide occurred in the year 2013. The majority (56%) of the reported cases in 2013 occurs in Southeast Asia and Western Pacific region, among them half are from India. On the other hand, Europe and the United States show a decline in the incidence of TB over the last decade, comprising only 7% of reported cases in 2013 collectively. ITB makes 1-3% of all TB cases, and 11% of extra pulmonary TB cases. ITB is more prevalent among females in Pakistan, West Africa, and Turkey, however, in other regions like China, Singapore, India and United Kingdom (UK), the ratio is either equal or opposite (1).

Crohn's disease traditionally reported as a disease of western countries with the highest incidence in Australia, Canada and UK is now getting more prevalent in Asia as well. More than 100% rise in the incidence of CD is witnessed in Japan, Korea, and Hong Kong over last 2 decades (1, 2). The proportion of males is significantly higher in CD (4).

Clinical manifestations

ITB usually has a symptom duration of a month to a year before diagnosis (2). CD manifests a relapsing and remitting course with a duration of illness even longer (1, 3). Abdominal pain, fever, and fatigue are the nonspecific symptoms shared by both conditions. However, night sweats, weight loss, anorexia and a light fever in the afternoon are more frequently associated with ITB, while malabsorption and protein loss indicates CD. Alteration in bowel habits is observed in both, but constipation is more frequent in ITB whereas chronic diarrhea is a feature of CD (3). Similarly, ascites, small bowel obstruction, and peritoneal/pulmonary involvement denote ITB and presence of bleeding per rectum, perianal involvement and extraintestinal manifestations (EIMs) are characteristics of CD. Presence of concomitant primary sclerosing cholangitis (PSC) may favor CD. Nonetheless, EIMs should be inferred with caution as TB can also infect joints, eyes, skin, liver and other organs in one third of patients (2). Strictures, perforations, and fistulas are again observed in both conditions (1). History of TB contact in family may be the clue for TB, similarly a family history of IBD can also be observed in 10% CD patients (2).



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Endoscopy

Although ITB and CD can affect any part of GIT, however the favorite site for both ITB and CD is ileocecum, therefore ileocolonoscopy is the initial procedure of choice. Involvement of proximal GIT and distal colonic segments favors CD (3), while involvement of less than four bowel segments favors ITB. Presence of transverse ulcers, nodularity, mass-like hypertrophic lesions, patulous/fixed-open ileocecal valve, pseudopolyps or scars signifies ITB. On the other hand, anorectal lesions, longitudinal or aphthoid ulcers, and cobblestoning are characteristics of CD (1, 3).

In patients with normal ileocolonoscopy, examination of small bowel is required with capsule endoscopy (CE) or enteroscopy. Capsule endoscopy (CE) is a safe and non-invasive modality for the diagnosis of CD providing an additional diagnostic yield of 25%-40% over other modalities (2). The sensitivity and specificity of CE for the diagnosis of CD is around 100% and 91% respectively (5). CE can visualize small ulcers and early inflammatory lesions. CE can also be used in followup patients to assess treatment response and mucosal healing. Limitations of CE include inability to take biopsies and risk of obstruction in stenosing CD. A patency capsule can be used prior actual examination in patients with high risk of retention. Literature is very scanty on use of CE in ITB. The described features of ITB on CE include multiple scattered short (<1-2cm), shallow, oblique or transverse mucosal ulcers with a necrotic base and irregular geographic borders in the jejunum and ileum (2, 5).

Enteroscopy (spiral, double balloon or single balloon) can visualize most of the small intestine by combined ante-grade and retrograde approaches with equivalent diagnostic yield as that of CE. Enteroscopy has an additional advantage of taking biopsies and performing therapeutic interventions such as stricture dilatation. However, it is more invasive than CE and need to be performed under anesthesia (2, 5).

Histology

Granulomatous inflammation is the core feature of both diseases under a microscope. In ITB, granulomas are larger (>400 µm) with caseation, confluence, involving more than four sites synchronously and located within the mucosa, submucosa or granulation tissue. Whereas in CD, they are infrequent (<5), smaller (<200 µm), poorly organized, isolated/discrete, more common in recto-sigmoid and distant

from mucosal changes (1). The sensitivity and specificity of confluent granulomas to distinguish among ITB and CD is reported around 38% and 99% respectively, while the same for the presence of epithelioid histiocytes is 41% and 94% respectively (6).

Newer surface markers used for differentiating the two entities include a monoclonal antibody against, for example, Mycobacterium tuberculosis complex (anti-VP-M660) and CD73 expression in tuberculous granulomas (1). Syndecan-1 (SDC1) and its endo-beta-D-glucuronidase Heparanase (HPA) functions as an integral membrane protein and are associated with the preservation of intestinal barrier function. In CD patients, SDC1 were found to be significantly decreased in mucosa and increased in serum, whereas HPA levels were elevated in both mucosa and serum (3).

Laboratory

Anemia, leukocytosis, thrombocytosis, hypoalbuminemia, and high erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are the common inflammatory markers shared by both conditions (3).

Because of the unsatisfactory analytic performance of tuberculin skin test and the time-consuming culture for acid-fast bacilli (AFB), microbiological diagnosis necessitates the employment of innovative tools. Interferon (IFN)-γ release assays (IGRA) which initially were introduced for the diagnosis of latent TB infection (3), are now widely available and can diagnose ITB with a sensitivity of 81% and specificity of 85% (1). The serological antibodies used for CD include anti-Saccharomyces cerevisiae antibody (ASCA) which give a sensitivity of 33% and specificity of 83% to diagnose CD. Because of its equal positive rate in ITB, ASCA cannot be used alone to distinguish ITB and CD. Therefore using a combination of IGRA and ASCA would be a better approach in the determination of the disease (7). A positive ASCA and negative IGRA has a sensitivity of 44.4% and specificity of 96% to diagnose CD (1).

Microbiology

Definitive diagnosis of ITB requires identification of the bacterium in tissue. This can be achieved by using Ziehl-Neelsen stain/AFB smear, culture or by polymerase chain reaction (PCR) assay. However the utility of these tests is limited as AFB smear is positive in less than 30% cases, while culture is time-consuming with a yield of only 25 – 35% (3). PCR can detect M. tuberculosis DNA in biopsy or

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stool samples giving an advantage of early diagnosis within 48 hours as compared to the culture time of 6 weeks with a sensitivity and specificity of 64.1% and 100% in biopsy material and 79% and 88% in stools, respectively (1).

Radiology

CT enterography is in use to differentiate the two diseases since late 1990's. Focal bowel involvement is a feature of ITB while CD is favored by the presence of segmental involvement. Other important signs to predict CD include asymmetric mural pattern, mural stratification, left colon involvement, the comb sign (most suggestive) and fibro-fat-proliferation. Whereas presence of exophytic soft tissue masses, calcified or necrotic lymph nodes of >1cm size along the right colic artery dictate ITB. Visceral fat area and visceral fat to subcutaneous fat ratio can also help in differentiating the two entities, however presence of fistula and abscess does not determine the etiology (1). Necrotic lymph nodes and comb sign on abdominal CT had the best diagnostic accuracy in differentiating CD and ITB in a meta-analysis (8). In order to avoid radiation exposure, Magnetic resonance enterography (MRE) is a good alternative with reported sensitivity and specificity of 81% and 86% as compare to 76% and 85% by CTE, respectively (5).

Barium studies can also help in distinguishing the two disease by showing short and concentric strictures with prestentotic dilatation in ITB, while long and eccentric strictures without any proximal dilatation (unless there is co-existing fibrosis) in CD (3).

Diagnostic models

Numerous analytic models were proposed by a grouping several distinctive features discussed earlier. The model proposed by Makharia et al gives a discriminating capability of 89.2% using the factors of weight loss as a prognosticator of ITB and focally enhanced colitis, the involvement of sigmoid colon and blood in stool as predictors of CD (9). Another model proposed by Lee et al provides diagnostic accuracy of 87.5% by using the parameters of involvement of fewer than four segments, patulous ileocecal valve, transverse ulcers and pseudopolyps for ITB while anorectal lesion, longitudinal ulcers, aphthoid ulcers and cobblestoning for CD (10). By using night sweats and granuloma for ITB and longitudinal ulcers for CD, Yu et al proposed a score which distinguished 86% of entire cases (11). Involvement of rectum, longitudinal ulcers and cobbleston-

ing for CD whereas fixed-open ileocecal valve, transverse ulcer and rodent ulcer for ITB also gave an accuracy of 82.5% (12). Recently a Bayesian model for differentiating ITB from CD was proposed based on a meta-analysis of 38 studies comprising 1,589 ITB and 2,117 CD patients. This was later validated by gender, clinical manifestations, endoscopic and pathological findings in 59 patients giving sensitivity, specificity, and accuracy for diagnosis of ITB up to 90.9%, 92.6% and 91.8% respectively (4). A proposed diagnostic algorithm is shown in figure 1 and comparison of different features is mentioned in table 1.

Approach in a patient where a differentiation between Intestinal Tuberculosis and Crohn's disease cannot be made

ITB and CD treatment diverges substantially. Inappropriate treatment can cause irreparable damage in view of immune-modulators and biological agents used in CD. Moreover, needless anti-TB treatment (ATT) not only leads to the development of drug resistance but also delays proper management. However, in real world scenario, empirical ATT can help in solving this mystery. Patients having doubtful IBD with negative PCR and culture or suspicious CD with positive IGRA result should be given a therapeutic trial of ATT. Clinical and endoscopic improvement after 2-3 months of ATT confirms the diagnosis of ITB and hence full course should be completed. However, every effort should be made to reach the diagnosis before starting empirical ATT (1).

Tuberculosis in patients requiring anti-TNF alpha treatment for Crohn's disease

Due to the core act played by TNF in granuloma formation and host response against infection, drugs that inhibit TNF hampers a person's ability to confiscate latent TB. There is a 5-fold increased risk for reactivation of TB during the first year of anti-TNF treatment. Therefore all IBD patients eligible for anti-TNF treatment should be screened for latent TB. A preventive chemotherapy should be administered in case of past exposure or untreated TB even in the absence of positive latent infection tests. This may include a course of isoniazid alone for 6 or 9 months, rifampicin alone for 4 months, or a combination of isoniazid and rifampicin for 3 months. Although after 3 weeks of preventive chemotherapy, anti-TNF can be commenced, some authors endorse that preventive chemotherapy should be finished prior to the commencement of anti-TNF therapy (3).

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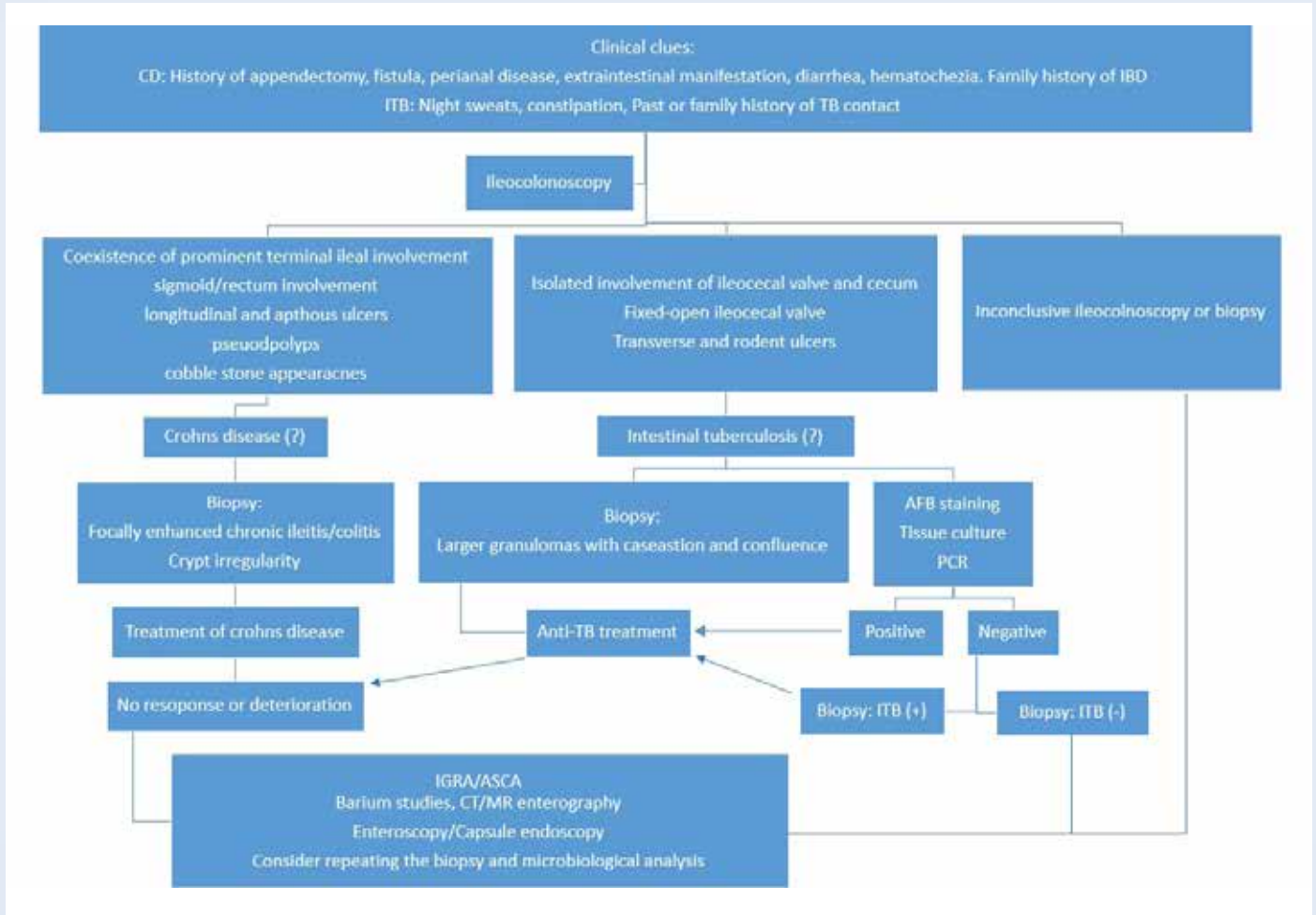


Figure 1. A Proposed algorithm for the differential diagnosis of Crohn's disease and intestinal tuberculosis adapted from *onal et al (3)*. ITB: Intestinal tuberculosis; ASCA: Anti-*Saccharomyces cerevisiae* antibody; IGRA: Interferon (IFN)- γ release assays; AFB: Acid fast bacilli; PCR: Polymerase chain reaction.

In summary, there are many overlapping features in patients with ITB and CD. There is no single feature which can distinguish among the two entities, therefore diagnosis depends on several facets. In order to avoid unnecessary treatment and delays, every possible measure should be taken to establish the diagnosis. In cases of uncertainty, novel methods should be used to improve diagnostic accuracy. A multidisciplinary approach may also help in reaching towards a conclusion. A trail of ATT can be considered in endemic areas of TB when diagnostic dilemma continues.

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Table 1. Clinical, endoscopic and histological differentiation between intestinal tuberculosis (ITB) and Crohn's disease (CD), taken from Moka et al (5).

Variables		ITB (%)	CD (%)
Clinical features	Chronic diarrhea	20-40	60-80
	Blood in the stools	10-20	50-70
	Abdominal pain	90	60-80
	Constipation	50	10-30
	Partial intestinal obstruction	50-60	20-30
	Perianal disease	5	30-80
	Fever	40-70	30
	Loss of appetite	40-80	40-60
	Weight loss	60-90	50-60
	Extra-intestinal manifestations	10	20-50
Involvement of Intestine	Anal canal	<5	15-50
	Rectum	10-20	40-60
	Sigmoid colon	5-10	10-50
	Descending colon	5-10	10-50
	Ascending colon	40-60	50-70
	Ileocaecal area	70-90	60
	Ileum	10-20	20-40
Endoscopic features	Aphthous ulcers	5-10	30-50
	Linear ulcers	5	20-30
	Deep ulcers	50-70	30-40
	Nodularity	50	20
	Cobblestoning	None	15-20
Histological features	Granuloma	30-60	30
	Necrosis in the granuloma	10-30	None

Cancer in IBD



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Introduction

The global prevalence of cancer is increasing, largely as more patients are living into old age. Therefore, gastroenterologists caring for patients with inflammatory bowel disease (IBD) increasingly are managing patients with cancer, or a previous history of cancer. The contribution of the disease itself or of treatment for the disease have to be considered. The message is inevitably mixed: despite an undoubted risk of cancer increasing as a consequence of disease, the absolute risk remains small, so the risk needs to be put in perspective. Treatment can reduce the risk of some tumours, but increase the risk of others. The two do not balance out, because the risks of undertreating IBD substantially outweigh the risks of treatment related cancer in most patients.

IBD and solid organ cancer

Colorectal cancer

Patients with IBD are at increased risk of developing colorectal cancer (CRC), which, in the case of ulcerative colitis (UC), varies with the extent and duration of the disease, family history of CRC, and the presence/absence of primary sclerosing cholangitis. The absolute risk of CRC complicating UC has been overestimated in the past, owing to information obtained from hospital sources of patients with more extensive or severe disease. An analysis of all population-based studies found that the risk for CRC was increased 1.7 (95% confidence interval, 1.2-2.2) in all patients with IBD. Given that the absolute risk of colorectal cancer in the general population is 3-4%, then the absolute risk in patients with over a 30 year period is around 5-7%. Patients with persistently active colitis, especially extensive colitis are at higher risk while those with limited colitis or proctitis are at no increased risk.

The risk of CRC is highest in patients with dysplasia detected on colonic biopsies, especially high grade dysplasia.

Endoscopic surveillance and treatment tailored to the individual patient's risk factor profile are recommended by national and international guidelines. Proctocolectomy abolishes the risk of CRC. Treatment (see below) can reduce the risk if inflammation is controlled.

Anal, fistula-related, and ileo-anal pouch cancers

Anal cancer arising from perianal fistulas are a rare complication of Crohn's disease (CD). In an analysis of over 40000 patients with CD-associated cancer, the incidence of cancer related to CD-associated fistulas was 0.2/1,000 patient years. Fistula-related cancer is associated with signs and symptoms attributable to the fistula: in a review of 65 patients, the average duration of the involved fistula was 14 years and the mean delay of cancer diagnosis was 11 months. This means that every effort should be made to control inflammation from chronic fistulas and a high index of suspicion if pain develops in the absence of an abscess.

Extraintestinal cancer

The overall risk of cancer outside the gastrointestinal tract in patients with IBD is not increased relative to the general population. In an analysis of population-based studies comprising a total of over 17,000 patients with IBD there was no increased risk of cancer at any site in the IBD population (risk relative to the general population 1.10). However, analysis by individual cancer sites shows that patients with CD are more likely to develop cancers of the lung (risk relative to the general population 1.82, because patients with CD more commonly smoke), urinary bladder (relative risk 2.03 for the same reason), and non-melanoma skin cancers (relative risk 2.35, possibly related to azathioprine). UC is associated with an increased risk of liver-biliary tract cancers (relative risk 2.58 because primary sclerosing cholangitis is more common in UC) and leukaemia (relative risk 2.00 for reasons that are unclear), although their risk of developing lung cancer is reduced more than two-fold (relative risk 0.39, because fewer patients with UC smoke).

IBD and haematologic malignancies

According to the 2013 SEER database, the current life time risk of non-Hodgkin lymphoma (NHL) is 2.1%, and the 5-year survival rate is 69%. Corresponding figures for other haematological malignancies for Hodgkin lymphoma are 0.2% and 85% and leukaemia: 1.4% and 57%.

Cancer in IBD, continued.

IBD-specific risk factors

Early disease onset, male gender and age >65 are risk factors for haematologic malignancies in patients with IBD. The risk is increased by Epstein-Barr virus (EBV) infection and most patients who develop haematologic malignancies after initiating thiopurine therapy are EBV-positive. In the largest case-control study to date on lymphoma and IBD (80 lymphoma patients and 159 matched controls), male sex (relative risk 4.05) and current immunosuppressive therapy increased the risk (relative risk 4.20). The absolute risk, is however, very low.

Clinical presentation and diagnosis

The possibility of haematologic malignancies should be considered for any patient with IBD and persistent haematologic changes that are unresponsive to treatment, enlarged lymph nodes, liver or spleen. Fever, weight loss and night sweats are typical symptoms. In such circumstances, specialist haematologic consultation is advised. Diagnosis is generally made by examination of the peripheral blood film, bone marrow aspirate and CT scan or lymph node biopsy.

Prevention and risk reduction

There is no clear algorithm for identifying IBD patients at risk of developing haematologic malignancies. Given the increased risk in patients receiving immunomodulators, the risks of a combination of immunosuppressive therapies should be carefully considered in young men who are likely to require prolonged treatment. Some clinicians prefer methotrexate to azathioprine in young men, because there are fewer reports of haematologic malignancy on methotrexate, but this may simply reflect prescribing frequency. It should also be remembered that controlling active intestinal inflammation may reduce the risk of haematologic malignancies.

IBD and skin malignancies

Current estimates indicate that approximately 20% (one in five) of the general population will develop skin malignancies (melanoma and/or non-melanoma skin cancer, NMSC) in the course of their lifetimes. 91% of the 2% with melanoma will survive for 5 years after the diagnosis and an even higher proportion with NMSC.

IBD-specific risk factors

It is unclear whether IBD is an independent risk factor for melanoma, although it increases the NMSCs, possibly due to drug-induced photosensitivity and smoking among patients with CD. Squamous-cell carcinoma (SCC) and basal cell carcinoma (BCC) are the most common NMSCs occurring in IBD. Advanced age is associated with higher risk of NMSC.

Clinical presentation and diagnosis

The clinical presentation and diagnosis are similar to skin malignancies in patients without IBD, and no specific criteria are available for early diagnosis. Change in shape, bleeding from, or the development of itching in an established skin lesion should raise suspicion. Diagnosis is confirmed by biopsy by a dermatologist.

Prevention and risk reduction

Some clinicians advocate annual skin screening by a dermatologist for patients on thiopurine therapy, especially for those aged >50y. Advice to avoid prolonged sun exposure and the use of sunbeds as well as adequate sunblock protection is appropriate. Patients who have been successfully treated for skin malignancies are at risk for recurrence and need long term follow up, with careful consideration given to the need for any immunosuppressive therapy.

Malignancy related to IBD therapy

Cancers caused by immunosuppressant drugs represent a minority of the cancers observed in patients with IBD. The risk of cancer related to IBD therapy has been investigated in analyses of very large medico-administrative databases or large cohorts of patients, since reports from single centres (even those with several thousand patients) are too small to identify the risk. This helps put the absolute risk into perspective.

Thiopurines (azathioprine and mercaptopurine)

Thiopurines can promote cancer in a number of ways. They can produce mutations of cell DNA, impair tumour-cell immunosurveillance and reduce the number and/or function of immune cells that prevent cells chronically infected by Epstein-Barr virus from proliferating. The relative risk compared to those with IBD not on therapy in a 19000 patient French cohort was 1.68 and 1.41 in a large, population-based Danish study. The difference between these fig-

ures is related to the fact that BCCs were included among the cancers analysed in the French but not in the Danish study. Past exposure to thiopurines was not associated with any excess risk of cancer in either of these studies. Thiopurine therapy in patients with extensive UC for more than 10 years decreased the risk of colorectal cancer.

AntiTNF therapy (infliximab, adalimumab, certolizumab pegol, golimumab)

Tumour necrosis factor (TNF)-alpha is a cytokine produced by immune cells which exerts necrotizing effects on tumour cells in the laboratory. Inhibition of TNF-alpha has therefore been hypothesized to increase the overall cancer risk, possibly in combination with impaired immunosurveillance of tumour cells. Since 1995, several studies have investigated the cancer risk associated with TNF-alpha antagonists used in IBD. Most patients treated with these agents also used (or had used) thiopurines, so it is difficult to attribute the findings to anti-TNF therapy alone. Based on a pooled analysis of data from controlled trials of infliximab therapy for CD, the incidence of cancer (of any type) was similar in patients treated with infliximab and those who received placebo. A pooled analysis of data from trials of adalimumab in IBD also revealed no excess risk of cancer related to adalimumab monotherapy, but the risk was significantly increased in patients receiving adalimumab and thiopurines. A nationwide study in Denmark found no evidence that TNF-alpha antagonists increased the overall risk of cancer in IBD patients over a median follow-up of 3.7 years, but it should be remembered that combination therapy with infliximab and thiopurines is the rule rather than exception.

Management of IBD patients with history of malignancies

The lifetime risk of cancer is rising due to increasing life expectancy and the increased incidence associated with advanced age. Data from registries suggest that individuals who survive cancer are 14% more likely to develop a second malignancy than those in the general population, and the development of a first cancer during childhood increases the lifelong risk of a second malignancy 6-fold.

The effects of drugs used in IBD on the risk of malignancy progression or recurrence

In patients with IBD and a history of cancer, the risk of developing a new or recurrent cancer is increased 2-fold relative to that of IBD patients who have never had cancer, regardless of whether or not they receive immunosuppressants. Preliminary data on IBD and other immune-mediated inflammatory diseases (such as rheumatoid arthritis) demonstrate no obvious excess risk of developing a second (new or recurrent) cancer while being treated with anti-TNF therapy. Nevertheless, the sensible specialist will liaise with the patient's oncologist in making treatment decisions that involve starting or continuing immunosuppressive therapy in individual patients. In general, concerns have been overstated, although it would be considered prudent to withdraw thiopurines if a patient develops NMSC or lymphoma.

Influence of chemotherapy on IBD

Limited evidence suggests that IBD can be aggravated by some hormonal therapy, chemotherapy-induced mucositis (a rare complication involving inflammation of the mucous membranes), or immunotherapy (increasingly used for melanoma and some other tumours). In patients with active disease at cancer diagnosis, remission can be induced and maintained thanks to the immunosuppressant effects of cancer treatment, despite withdrawal of immunosuppressant therapy for IBD). The impact of targeted anti-cancer therapy on IBD remains unknown.

Conclusions

The threat or diagnosis of cancer causes understandable concern for patients with IBD. The risk, however, needs to be put into perspective: a rare event affecting 1 in 100 of patients with IBD remains a rare event even if the risk is doubled or trebled. The risk of colorectal cancer complicating IBD has been overstated. The risk relating to treatment represents a small proportion of cancers affecting IBD, but has also been overstated. Concerns should be discussed with the individual specialists and fortunately, for the large majority of patients, the benefits of effective treatment for IBD substantially outweigh individual risks.

Cancer in IBD, continued.

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Inflammatory Bowel Disease

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