Saudi Arabia consensus guidance for the diagnosis and management of adults with inflammatory bowel disease

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Abstract

Optimal management of inflammatory bowel disease (IBD) relies on a clear understanding and tailoring evidence-based interventions by clinicians in partnership with patients. This article provides concise guidelines for the management of IBD in adults, based on the most up-to-date information at the time of writing and will be regularly updated. These guidelines were developed by the Saudi Ministry of Health in collaboration with the Saudi Gastroenterology Association and the Saudi Society of Clinical Pharmacy. After an extensive literature review, 78 evidence-and expert opinion-based recommendations for diagnosing and treating ulcerative colitis and Crohn's disease in adults were proposed and further refined by a voting process. The consensus guidelines include the finally agreed on statements with their level of evidence covering different aspects of IBD diagnosis and treatment.

Keywords: Crohn's disease, diagnosis, guidelines, inflammatory bowel disease, management, Saudi Arabia, treatment, ulcerative colitis

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INTRODUCTION

The term inflammatory bowel disease (IBD) encompasses two clinical entities: ulcerative colitis (UC) and Crohn's disease (CD).[1] They result in chronic inflammation of the gastrointestinal tract and display heterogeneous clinical manifestations between patients and within an individual patient over time.[1]

IBD is prevalent in Saudi Arabia.[2] In 2012 the incidence was estimated to be 0.94 patients per 100,000 individuals during the past 20 years.[3] The incidence of UC was reported to be steady, whereas that of CD is increasing.[4] The clinical characteristics and morbidity in Saudi patients suffering from IBD were reported to be similar to patients with IBD in Western countries.[5]

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The mean age of onset of IBD is 25.5 ± 10.6 years.[5] However, a second smaller peak (~15% of cases) is reported at age more than 60 years, referred to as an elderly onset IBD.[6] Very early onset IBD also occurs in children less than 6 years of age. The differential diagnosis of IBD is widely heterogenous, and differentiation from certain conditions such as segmental colitis associated with diverticulosis or intestinal tuberculosis (ITB) might be very challenging.

To optimize treatment outcomes, clinicians need to understand and tailor evidence-based therapies for a particular patient. To unify practice, treatment guidelines should be tailored according to the population characteristics, finances, insurance status, availability of medications, and medical reimbursement policies in each country. To date, no guidelines or consensus recommendations are adopted in Saudi Arabia to match the local needs. Accordingly, these guidelines were created by a group of experienced gastroenterologists and clinical pharmacists in the country. We aimed to provide condensed guidelines of IBD management for different categories of patients, which clinicians could use as a tool to develop an individualized patient management plan. The current recommendations are based on the most up-to-date information at the time of writing and will be updated on a regular basis. Furthermore, the current recommendations are not intended to be used as rigid therapeutic protocols. They are also not meant to replace the sound clinical judgment of practicing physicians. Instead, they are designed to assist and advise health care practitioners who are managing patients with IBD.

METHODOLOGY

These guidelines for the management of IBD in adults were developed by the Saudi Ministry of Health in collaboration with the Saudi Gastroenterology Association (SGA) and the Saudi Society of Clinical Pharmacology (SCCP). A literature review of the current publications and international guidelines regarding IBD management was performed. This set of guidelines was based on recommendations from the European Crohn's and Colitis (ECCO),[6,7] the American College of Gastroenterology (ACG),[8,9] the American Gastroenterology Association (AGA),[10] and the British Society of Gastroenterology guidelines.[11]

After reviewing all the guidelines generated by the literature search, expert opinion-based recommendations for the diagnosis and treatment of UC and CD were proposed and further refined by a voting process. [6,8-11] A committee composed of six expert gastroenterologists and six experienced clinical pharmacists reviewed the recommendations, suggested revisions, and commented on the statements, after which the specific statements were revised. The quality of evidence was considered as "high" if the data existing in the literature was driven from high-quality evidence-based studies (i.e., multiple double-blinded multicentric randomized controlled trials [RCT]) and, accordingly, further research was thought to be very unlikely to change the confidence in the estimate of effect. The quality of evidence was considered as "Moderate" if the data existing was driven from clinical trials and further research was thought to likely have a substantial impact on the confidence in the estimate of effect and may change the estimate. Data driven from weak studies were considered to have a "low" quality of evidence (i.e., further research was thought to very likely have a substantial impact on the confidence in the estimate of effect and is likely to change the estimate), and statements with "low" quality of evidence were removed from these consensus recommendations. The strength of recommendation was considered "very strong" if at least 80% of the panelists agreed to the statement, and was considered "strong" if 50% agreed.

RESULTS

The consensus includes 78 statements focused on the diagnosis and medical treatment options of IBD. The group supported the use of biochemical markers (C-reactive protein [CRP] and fecal calprotectin), ileo-colonoscopy with multiple biopsies, and cross-sectional imaging as important tools for a definitive diagnosis. Several classification systems were endorsed for different phenotypes of IBD among adults. The group reached an agreement on positioning of corticosteroids, 5-aminosalicylates (5-ASA), immunosuppressants, small molecules, and biologic agents as treatment options for IBD (both UC and CD). The treat-to-target (T2T) strategy was chosen as the core treatment strategy for IBD. Most of the statements were supported by high-quality evidence.

CONSENSUS RECOMMENDATIONS

Diagnosis and classification of CD and UC in adults

General diagnostic considerations

Statement 1: There are no precise criteria for diagnosing CD or UC. A combination of clinical, biochemical, endoscopic, radiographic, and histologic criteria is used to diagnose CD or UC.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

IBD includes a variety of intestinal disorders with an unclear etiopathology but similar clinical

manifestations.[12] The most representative entities are UC and CD.[12] UC is a chronic inflammatory disease characterized by mucosal inflammation starting distally in the rectum, with continuous extension proximally for a variable distance, often with an abrupt demarcation between inflamed and non-inflamed mucosa.[12] CD is a complex chronic inflammatory gastrointestinal condition with variable age of onset, disease location, and behavior.[13]

The prevalence of IBD increased from 0.9% in 1999 to 1.3% in 2015 in the adult population in the United States of America (USA).[14] An incidence rate ranging from 9.9/100,000 to 70.2/100,000 individuals per year was reported in 2014 in the USA.[15] In the Arab world, the incidence rate was estimated to be 2.33/100,000 individuals per year for UC and 1.46/100,000 individuals per year for CD.[2] In Saudi Arabia, the reported incidence rates of IBD ranged from 0.32/100,000 individuals per year to 1.66/100,000 individuals per year.[16,17]

The diagnosis of IBD is based on a combination of clinical, biochemical, endoscopic, radiographic, and histologic parameters.[18] Genetic and serological testing are not currently recommended as limited evidence supports their role in confirming IBD diagnosis.[19] Although the diagnosis of IBD can be challenging, some of the presenting symptoms may raise the suspicion of IBD. These may include hematochezia, diarrhea, tenesmus, and abdominal cramping.[20] However, these symptoms are not specific for IBD. Infectious etiologies, such as tuberculosis (TB), *Escherichia coli*, *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, and amebiasis, may present with similar symptoms. This should be considered before a final diagnosis of IBD is made.[21]

Statement 2: We recommend using the Red Flags Score (RFS) to help differentiate irritable bowel syndrome (IBS) from CD.

Quality of evidence: High; Grade: High.

Strength of recommendation: Strongly recommended (50% of panel strongly agreed).

The RFS is a screening method developed to identify patients at a higher risk of having CD rather than IBS.[22,23] Danese *et al*.[23] developed a 21-item survey that was administered to healthy subjects, patients with IBS (non-CD group), and patients with recently diagnosed (<18 months) CD. The authors concluded that a minimum RFS value of 8 was highly predictive of CD diagnosis with sensitivity and specificity bootstrap estimates of 0.94 (95% confidence interval 0.88–0.99) and 0.94 (0.90–0.97), respectively.[23] Furthermore, the association between CD diagnosis and a RFS value of ≥8 corresponded to an OR of 290 ($P < 0.0001$) in this study.[23] A more recent study from Saudi Arabia outlined the association between an elevated RFS in patients with IBS who did not undergo diagnostic ileo-colonoscopy, and the lack of specialized gastroenterological evaluation, thus, appealing for early specialized referrals.[23,24] The RFS was developed and is used to diagnose CD, but it cannot be applied to cases with UC.

Statement 3: Genetic and serological tests are not currently recommended for diagnosing CD or UC. Complementary studies should focus on risk stratification and disease activity evaluation at the time of diagnosis.

Quality of evidence: Moderate; Grade: Moderate.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

Genetic and serological testing for the purpose of IBD diagnosis is not recommended as limited evidence supports their role in this setting.[19] Clinicians should not use serological antibody testing to establish or rule out the diagnosis of IBD.[9,25] To date, the data are limited about the accuracy of the tests available.[26] Accordingly, no valid biomarker exists that can differentiate colonic CD from UC.[26] Reese *et al*.[27] conducted a meta-analysis to evaluate the diagnostic precision of anti-*Saccharomyces cerevisiae* (ASCA) and perinuclear antineutrophil cytoplasmic antibodies (pANCA) in IBD. In their study, they also assessed the ability of these two markers to differentiate between UC and CD. Their results denoted that ASCA and pANCA antibodies are specific but not sensitive for differentiating UC and CD in adults. Similarly, the additional diagnostic value of other serum biomarkers such as antibodies against exocrine pancreas, anti-granulocyte macrophage colony-stimulating factor antibodies, or anti-microbial antibodies, is limited.[28] Likewise, there are no available genetic markers that can accurately diagnose IBD or differentiate UC from CD.[29]

Statement 4: Fecal calprotectin (FC) is a non-invasive disease activity measure that may be used to screen for IBD, assess treatment response, and predict recurrence.

Quality of evidence: High; Grade: High..

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

FC, a neutrophil-derived protein, appears to be the most sensitive marker of intestinal inflammation in IBD.[30-33] FC values correlate well with endoscopic indices of disease activity.[30-33] Hence, they can be used for serial monitoring of disease activity and assessment of treatment response.[30-33] FC values can even serve in predicting clinical recurrence or sustained remission.[30-33] A cutoff value of FC 100 μg/g was found to have a 100% specificity and 88% sensitivity for endoscopic activity in UC and a 67% specificity and 100% sensitivity in CD.[34] Although it is of significant value in detecting colonic inflammation in IBD, FC is less reliable and sensitive in a sub-population of CD with limited small bowel disease.[35,36]

Statement 5: Ileo-colonoscopy with biopsies from inflamed and non-inflamed segments is necessary for suspected IBD. If the patient has severe acute colitis, a flexible sigmoidoscopy is preferred.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

Ileo-colonoscopy is considered as the gold standard investigation for diseases of the large bowel, as it allows direct mucosal visualization, biopsy, and therapeutic intervention of the colon and terminal ileum. During ileo-colonoscopy, at least two biopsies should be taken from inflamed areas to diagnose UC and CD.[37] Additional biopsies should be taken from both affected uninflamed segments of the colon and the rectum. This will assist in establishing the macroscopic and microscopic extent of the disease.

Sigmoidoscopy with biopsies may offer a suitable alternative initial modality in patients with severe UC because of the high risk of perforation.[38] An ileo-colonoscopy should still be performed after instituting effective therapy to determine disease extension, degree of inflammation, and to rule out CD.[38]

Statement 6: There are no endoscopic features unique to CD or UC. The most important endoscopic features of UC are confluent and continuous colonic involvement with clear demarcation of inflammation and rectal involvement. The most crucial endoscopic features of CD include terminal ileal involvement, perianal involvement, presence of fistulae, strictures, and discontinuous lesions.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (90% of panel strongly agreed).

Endoscopic features of UC include continuous inflammation starting in the rectum with friable mucosa, granularity, and loss of vascular markings.[39] Deep ulcers and bleeding are associated with more severe cases.[39] Endoscopic features suggestive of CD include mucosal nodularity, ulcerations (both aphthous and linear), presence of fistulae, and strictures.[40]

Statement 7: Features of chronicity on histological examination of the mucosa such as crypt architectural distortion and chronic inflammation are necessary to diagnose IBD.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

Histological examination of the mucosa plays an essential role during the diagnosis of IBD. For example, infectious colitis is distinguished from IBD by the presence of intact crypt morphology and acute inflammatory process. Features of chronicity such as crypt architectural distortion and chronic inflammation are necessary to diagnose IBD.[37] Histological features can also aid in differentiating between UC and CD through the presence of patchy disease and granulomas, which are suggestive of CD rather than UC.[41] However, in UC patients, basal plasmacytosis has been identified as the characteristic histological feature with the best predictive value for UC diagnosis.[42] Generalized mucosal or crypt architectural deformation, mucosal atrophy, and villous mucosal surface can develop after 1 month of clinical presentation.[37,41]

Statement 8: Cross-sectional imaging modalities, including magnetic resonance, computed tomography (CT), and intestinal ultrasonography (IUS), are recommended for radiological evaluation of the small bowel in patients with IBD.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (90% of panel strongly agreed).

To assess the small bowel, either magnetic resonance enterography (MRE) or computed tomography enterography (CTE) should be performed. Both studies require the patient to drink a large volume of neutral contrast, which is used to help highlight inflammation, strictures, ulcers, and cobblestone appearance of the intestinal wall.[43] Cross-sectional imaging can also identify extraluminal findings, such as fistulae and mesenteric thickening. A recent meta-analysis showed that the sensitivity and specificity for CTE were 87% (95% confidence interval [CI], 78-92%) and 91% (95% CI, 84-95%), respectively, and 86% (95% CI, 79-91%) and 93% (95% CI, 84-97%), respectively, for MRE.[44] As opposed to MRE, CTE involves the administration of ionizing radiation to patients, which is important because disease monitoring usually occurs on a lifelong basis for patients with IBD, and the cumulative dose of radiation can be significant over decades.

In contrast, MRE often requires the patient to stay in a small, enclosed space, which can induce claustrophobia. Furthermore, it does not provide detailed data about perianal disease. Dedicated MRI of the pelvis is the best current technique to evaluate perianal disease,[45] with a 97% sensitivity and 96% specificity for diagnosing anal fistulae in CD.[46] CT has advantages that include lower cost, less procedure time, more suitable procedure, widespread availability, less need for anesthesia, and is more suitable for patients with contraindications for MRI. Additionally, CT scanning is more sensitive in determining the presence of abscesses.[47] Ultrasonography also avoids the use of ionizing radiation in the evaluation of the bowel. It is primarily used to diagnose bowel wall thickening or differential diagnosis between inflammatory and fibrotic strictures. Small bowel ultrasonography has a sensitivity of 89% and a specificity of 94.3% in the assessment of patients with known CD but is less accurate in detecting proximal lesions.[48]

UC diagnosis

Statement 9: Patients with persistent or recurrent hematochezia and urgency should be suspected of having UC after excluding infectious etiologies.

Quality of evidence: High; Grade: High

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

More than 90% of patients with active UC report having rectal bleeding. Associated symptoms generally reflect the severity of mucosal disease and may differ according to disease extent.[49] Loose stools for more than 6 weeks most likely reflect extensive UC rather than infectious diarrhea.[50] Patients with active UC also complain of rectal urgency and tenesmus. Therefore, these persistent or recurrent symptoms should raise suspicion of UC.

Statement 10: In individuals suspected of having UC, stool testing is recommended to rule out enteric infections, including special testing for *Clostridioides difficile* (C. diff) infection.

Quality of evidence: High; Grade: High

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

Stool specimens should be obtained to exclude common pathogens. Specific *C. difficile* (C. diff) assays should be performed because the infection with this pathogen is a significant risk factor for complications, hospitalization, and mortality.[51] Furthermore, numerous studies have outlined the link between *C. diff* infection and IBD relapse.[52-54] Although several techniques exist to diagnose *C. diff* infection, testing is commonly done by enzyme-linked immunosorbent assay for *C. diff* glutamate dehydrogenase and TcdA and/or TcdB[55] or polymerase chain reaction (PCR) for TcdB gene.[56] The sensitivity of the PCR is high in detecting the presence of toxigenic *C. diff* infection, even in asymptomatic cases. Thus, it is recommended by most experts to be done on a diarrheal stool sample.[56]

Statement 11: If UC is identified by sigmoidoscopy, a future complete ileo-colonoscopy is recommended to determine the extent and severity of inflammation and to rule out CD.

Quality of evidence: High; Grade: High

Strength of recommendation: Very strongly recommended (80% of panel strongly agreed).

While flexible sigmoidoscopy might be the initial diagnostic modality for UC, performing a full ileo-colonoscopy is essential within the first year.[57] This will confirm the diagnosis, evaluate the extent and severity of the disease, differentiate between UC and CD, and help tailor an appropriate treatment plan.[57]

CD diagnosis

Statement 12: In endemic areas such as Saudi Arabia, the differential diagnosis of ITB should be considered for individuals with suspected ileocecal CD.

Quality of evidence: High; Grade: High

Strength of recommendation: Very strongly recommended (80% of panel strongly agreed).

Patients with ileocecal CD can be misdiagnosed with ITB because of similarities in the presentation. A comprehensive assessment (history, physical examination, laboratory testing, endoscopy, histology, and radiological examinations) is needed to be able to make the distinction between the two etiologies. Night sweats, concurrent pulmonary tuberculosis, a positive tuberculin skin test, positive interferon-gamma release assay (IGRA) for TB, prominent abdominal lymphadenopathy, ascites, transverse-appearing ulcers, and a patulous ileocecal valve are all signs suggestive of ITB.[58] There is no available validated method that can accurately differentiate between CD and ITB; however, several key elements found on colonoscopy, serology, and radiological examinations can help the differential diagnosis between the two entities.

Previous research showed that ITB lesions are characterized by both inflammation and proliferation, whereas CD lesions are characterized by inflammation of the entire intestinal wall thickness leading to ulceration.[59] Other differentiating features include wider lesions and more frequent rectal involvement in CD compared to ITB. The lesions in ITB are usually confined to the right colon.[59] In ITB, necrotic lymph nodes and contiguous ileocecal involvement are common. A meta-analysis conducted by Du *et al*.[60] comprising 692 patients showed that the most reliable histological characteristics in distinguishing ITB from CD were caseating necrosis, confluent granulomas, and ulcers bordered by epithelioid histiocytes. Visualization of a patulous ileocecal valve, post-inflammatory polyps, transverse ulcers and scars, and involvement of less than four colonic segments are suggestive findings of ITB.[60] The colonoscopy parameters that are considered supportive of a CD diagnosis include anorectal lesions, longitudinal ulcers, aphthous ulcers, and cobblestone appearance.[60]

A positive ASCA serology and proximal small bowel disease may indicate CD, whereas a positive IGRA test and typical pulmonary lesions could point to TB.[61] The use of a scoring system that combines radiological findings and laboratory results was reported to have an accuracy rate of 81.2% and a sensitivity of 97.5% for differentiation between ITB and CD.[61] TB PCR performed on intestinal biopsies may aid in the distinction between the two diseases.[62] The sensitivity of TB PCR performed on endoscopic biopsy was reported to range from 5.8 to 45.5%, and the specificity ranged from 88.1 to 100% based on the type of kits used.[62]

Other diagnostic tests that can be used to diagnose ITB are the acid-fast bacilli (AFB) staining and mycobacterium TB culture.[63,64] Staining AFB with *Ziel Nelson* method is a highly specific method in evaluating ITB (specificity 100%).[64] However, the sensitivity is low (17.3–31%). Using a culture from a tissue biopsy is the gold standard for diagnosing ITB.[65] It has a very high specificity (almost 100%), a positive predictive value (PPV) of 100%, a negative predictive value (NPV) of 38.3%, but a very low sensitivity (9.3%).[64]

Despite the variety of methods for diagnosing ITB in patients with IBD, many cases remain challenging.[65] Some authors suggest starting empirical anti-tuberculous medications in such suspected cases, but strong evidence for this practice is lacking.[65]

Statement 13: In contrast to asymptomatic newly diagnosed patients with CD, adult patients with upper GI symptoms should undergo esophagogastroduodenoscopy (EGD).

Quality of evidence: Moderate; Grade: Moderate.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

Patients with IBD who have upper gastrointestinal symptoms such as nausea, dyspepsia, and vomiting would benefit from an EGD.[66] The debate about using EGD for asymptomatic patients with CD is continuing, especially because of the recent evidence suggesting a higher prevalence of upper GI involvement in asymptomatic CD.[66] In a recent study from Saudi Arabia involving 78 patients with CD, 19 out of 78 patients (24.4%) had histologically confirmed CD involving the upper

gastrointestinal tract (3 esophageal, 16 gastric, and 9 duodenal), of which 52.6% were symptomatic.[67] If the intestinal histopathological findings are not conclusive in a suspected case of CD, an EGD and a biopsy from focal gastritis may help support the diagnosis.[68]

Statement 14: If ileo-colonoscopy is normal, in a patient suspected of having CD, EGD and cross-sectional imaging of the abdomen are recommended

Quality of evidence: High; Grade: High

Strength of recommendation: Very strongly recommended (80% of panel strongly agreed).

As previously mentioned, EGD with evidence of focal gastritis from a histopathological examination may support the diagnosis of CD.[68] Furthermore, the use of cross-sectional imaging can further delineate the diagnosis of CD.

Statement 15: Small intestine video capsule endoscopy (VCE) is an alternative to cross-sectional imaging for patients with a clinical picture of CD and a normal ileo-colonoscopy.

Quality of evidence: Moderate; Grade: Moderate.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

Small intestine VCE is a sensitive diagnostic modality that can visualize small intestinal mucosal abnormalities.[69] The diagnostic capabilities of VCE appear to be superior to MRE or small intestine contrast ultrasound when evaluating the proximal small bowel.[69]

Statement 16: We recommend assessing the risk of retention before using VCE when stenotic disease is suspected in CD

Quality of evidence: Moderate; Grade: Moderate.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

Contraindications for VCE include gastrointestinal obstruction, strictures, and swallowing disorders.[70,71] The reported retention rates of VCE in patients with established CD range from 2 to 13%. In patients with suspected CD, the rate is lower and estimated to be approximately 1.5%.[72] To confirm small intestine patency before performing VCE, a patency capsule can be used to exclude significant small bowel stenosis.

Statement 17: The diagnosis of CD should be suspected if three or more ulcers were found in the small intestine after excluding the use of non-steroidal anti-inflammatory drugs within a month of testing.

Quality of evidence: Moderate; Grade: Moderate.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

Limited data exist regarding the number of ulcerations found during enteroscopy that are suggestive of CD. Mow *et al*.,[73] in their study using wireless capsule enteroscopy, reported that the presence of three or more lesions could be diagnostic of CD. About 26% of the cases in their study had three or more lesions. However, the sample size of this study ($n = 50$) was small, and the sensitivity and specificity of using the three ulcers threshold were not reported. In a more recent study including a larger cohort of 102 patients, Tukey *et al*.[74] reported that using a cutoff value of more than three ulcers had a sensitivity of 77% and a specificity of 89%. The PPV was 50%, whereas the NPV was 96%.[74] This indicates that the use of a more than three ulcers cutoff value makes the diagnosis of CD probable but not definite.

Statement 18: Device-assisted enteroscopy may be used to verify the diagnosis of CD in patients with negative upper and lower endoscopy and features suspicious of CD on MRE or small bowel VCE.

Quality of evidence: Moderate; Grade: Moderate.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

Monteiro *et al*.[75] showed that 25% of patients with unclassified IBD were found to have small bowel involvement consistent with CD on VCE examination. Still, approximately one-third (37%) of them remained unclassified during further follow-up. This data supports the need for further assessment of device-assisted enteroscopy as a diagnostic tool for CD. This approach also aids in acquiring tissue for histopathological examination that could support the diagnosis.

Statement 19: CD should be suspected in patients with recurrent perianal abscesses or complicated fistulae.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

Perianal manifestations of CD occur in around 25% of patients, and manifest in fistulae and abscesses. Perianal manifestations of CD occur more frequently in patients with isolated colonic involvement.[76] It can also be the first manifestation in CD, and the patient might have a normal ileo-colonoscopy.[77,78] Clinical and imaging findings are essential for diagnosing and characterizing perianal disease.

There are two types of fistulae: simple, if they are superficial, involve <30% of the external sphincter, and have a single external opening without complications. Complex fistulae have high output with multiple external openings and tend to be associated with abscesses, rectovaginal fistulae, or anorectal strictures.[79] Complex fistulas, in particular, should warrant further evaluation for the likelihood of being a case of CD presenting initially with perianal symptoms.[79,80] Several imaging modalities are used for the diagnosis of perianal CD, including plain X-ray and contrast fisulography, CT, anal endosonography, and MRI.[81] MRI is the modality of choice.[81] Evaluation of coexisting luminal CD with ileo-colonoscopy and small bowel assessment should be routinely performed in all patients with perianal CD. The endoscopic examination will reveal the presence of internal openings and complications, such as strictures or cancer.[82]

Classification of IBD

Statement 20: We recommend using the Montreal classification for adults and the Paris classification for adolescent patients to describe the IBD disease extent and phenotype.

Quality of evidence: High; Grade: High

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

The Montreal classification [Table 1] was introduced as an attempt to describe the extent and behavior of CD in more detail and included a classification system for UC.[83] Since its introduction, several studies have assessed its inter-observer reliability and validity. The results showed good inter-observer reliability for disease location but fair/moderate reliability for upper GI involvement.[83,84] Furthermore, Montreal classification did not appear to be a reliable classification system for disease severity in UC.[85]

The Paris classification of UC [Table 2] evaluates the disease's extent that is classified into E1, E2, E3, and E4. In E1, (ulcerative proctitis) the inflammation is confined to the rectum. In E2, the inflammation involves a portion of the colorectum that is distal to the splenic flexure. While in E3, the inflammation extends distal to the hepatic flexure, and in E4, the inflammation extends proximally to hepatic flexure.[86] Disease extent should be confirmed by mapping biopsies, as endoscopic appearance may undervalue the true

Table 1: Montreal classifications of UC and CD[83]

Montreal classification of UC		
Extent	E1	Ulcerative proctitis
	E2	Left-sided UC (distal to splenic flexure)
	E3	Extensive (proximal to splenic flexure)
Severity	S0	Clinical remission
	S1	Mild UC
	S2	Moderate UC
	S3	Severe UC
Montreal classification of CD		
Age at diagnosis	A1	<16 years
	A2	17- 40 years
	A3	>40 years
Location	L1	Ileal
	L2	Colonic
	L3	Ileocolonic
	L4	Isolated upper GI disease
Behavior	B1	Non-stricturing, non-penetrating
	B2	Stricturing
	B3	Penetrating
	P	Perianal disease modifier

UC=ulcerative colitis, CD=Crohn's disease

Table 2: Paris classifications of UC and CD[87]

Paris classification of UC		
Extent*	E1	Ulcerative proctitis
	E2	Left-sided UC (distal to splenic flexure)
	E3	Extensive (hepatic flexure distally)
	E4	Pancolitis (proximal to hepatic flexure)
Severity	S0	Never severe†
	S1	Ever severe†
Paris classification of CD		
Age	A1a	0 to <10
	A1b	10–17
	A2	17– 40
	A3	>40
Location	L1	Distal 1/3 ileal±limited cecal disease
	L2	Colonic
	L3	Ileocolonic
	L4a	Upper disease proximal to the ligament of Treitz
	L4b	Upper disease distal to the ligament of Treitz and proximal to distal 1/3 ileum
Growth	P0	Perianal disease modifier
	G0	No evidence of growth delay
	G1	Growth delay

UC=ulcerative colitis, CD=Crohn's disease. *Extent defined as maximal macroscopic inflammation.†Severe defined as a Pediatric Ulcerative Colitis Activity Index score >= 65

extent. Determining disease extent is critical for prognosis and the risk of undergoing colectomy. Disease extension is dynamic, and it may progress or regress with time. In the Paris classification of UC [Table 2], the severity of the disease is only classified to either S0 (never severe) or S1 (ever severe).[87,88]

Statement 21: We recommend using the Harvey–Bradshaw Index (HBI) to assess for and monitor clinical disease activity in CD.

Quality of evidence: High; Grade: High

Strength of recommendation: Very strongly recommended (90% of panel strongly agreed).

The HBI assesses clinical disease activity in CD.[89,90] The HBI comprises five clinical items, i.e., general well-being, abdominal pain, number of liquid stools per day, abdominal pain, and complications [Table 3].[91] The score does not include laboratory or biological tests.[91] An HBI score less than five is defined as clinical remission, HBI between 5 and 7 as a mild disease, HBI between 8 and 16 as moderate disease, and HBI >16 as severe disease.[88] The HBI is poorly associated with endoscopic disease activity.[92] An HBI of ≥4 was reported to have a sensitivity of 79% and a specificity of 61% for detecting active disease.[92]

Statement 22: We recommend using the Simple Endoscopic Score for Crohn's Disease (SES-CD) for assessment of CD endoscopic activity and response to therapy.

Quality of evidence: High; Grade: High

Strength of recommendation: Strongly recommended (100% of panel strongly agreed).

Simple SES-CD is based on the evaluation of five defined bowel segments (rectum, left and sigmoid colon, transverse colon, ascending colon, and terminal ileum), and in these segments, the presence and size of ulcerations and the extent of the inflammatory area and stenosis are assessed, then classified in severity as a score of 0–3. The scores for each individual segment are added together as a sum score [Table 4].[93] Although widely used, the SES-CD was not completely validated.[94] The score's reliability was tested in four studies, and the overall interclass correlation coefficient was 0.9815.[94] However, there was a potential bias in these studies, which jeopardizes the confidence of the results interpretation.[94]

Statement 23: In clinical practice, we recommend using the Mayo Score for UC as a composite evaluation tool for disease activity.

Quality of evidence: High; Grade: High

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

Table 3: The Harvey-Bradshaw Index[90]

Item	State	Score
General well-being	Very well	0
	Slightly below par	1
	Poor	2
	Very poor	3
	Terrible	4
Abdominal pain	None	0
	Mild	1
	Moderate	2
	Severe	3
Number of liquid stools per day	0-1 liquid stools	0
	2-3 liquid stools	1
	4-5 liquid stools	2
	6-7 liquid stools	3
	8-9 liquid stools	4
	10+ liquid stools	5
Abdominal mass	None	0
	Dubious	1
	Definite	2
	Definite and tender	3
Complications	None	0
	Arthralgia	1
	Uveitis	1
	Erythema nodosum	1
	Aphthous ulcers	1
	Pyoderma gangrenosum	1
	Anal fissure	1
	New fistula	1
	Abscess	1

Table 4: Simple Endoscopic Score for Crohn's Disease[93]

Severity	0	1	2	3
Ulcerations	None	Aphthous ulcers (<0.5 cm)	Large ulcers (0.5-2 cm)	Very large ulcers (>2 cm)
Ulcerated surface	None	<10%	10-30%	>30%
Inflamed surface	None	<50%	50-75%	>75%
Stenosis	None	Single, passable	Multiple, passable	Not passable

Composite clinical and endoscopic disease activity assessment in ulcerative colitis

Table 5: Mayo score[95]

	0	1	2	3
Stool frequency (above average)	0	1-2	3-4	>5
Rectal bleeding	None	Mild	Moderate	Severe
Endoscopic findings	Inactive	Mild	Moderate	Severe
Physician global assessment	Normal	Mild	Moderate	Severe

The Mayo Score combines clinical and endoscopic variables; stool frequency, bleeding, inflammatory activity on sigmoidoscopy, and overall physician assessment [Table 5].[95] A score decrease by three or more is usually taken as therapeutic success. For the assessment of endoscopic mucosal response, the endoscopic subscore is most often used, and endoscopic healing (EH) is defined as an endoscopic subscore of 0 or 1 (more recently an endoscopic Mayo subscore of 0 has been suggested).

Medical treatment of CD and UC

Treatment goals and the T2T strategy for CD and UC

Statement 24: To evaluate the response to therapy in active UC, a combination of clinical, endoscopic, and laboratory parameters should be considered.

Quality of evidence: High; Grade: High

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

In the absence of a validated definition of remission in UC, the treatment target is widely variable among different countries. Many clinical and endoscopic parameters were proposed for assessment of treatment response.[96,97] Using mucosal healing (MH) as a therapeutic target is controversial because of the implications for clinical practice. There is an ongoing need for a more objective endoscopic assessment and subsequent therapeutic escalation in asymptomatic patients.[98]

There is a lack of clear evidence about the importance of histological remission as well as endoscopic remission (deep remission)[99,100] Recent studies suggest that the presence of endoscopic and histological inflammation is predictive of future flares, lack of sustained remission, need for corticosteroids, and colectomy.[101,102]

Clinical and/or patient-reported remission (defined as the absence of rectal bleeding and return to regular bowel habit) paired with endoscopic remission (Mayo endoscopic subscore of ≤1) is becoming an increasingly popular accepted treatment target for UC among specialists.[103]

Recent recommendations from the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) indicate, as a short-term treatment goal, the normalization of CRP (to values under the upper limit of normal), and FC (to 100–250 μg/g), and the change of treatment plan if the target has not been achieved.[92]

Statement 25: We recommend using clinical response as an urgent target of treatment in adults as follows:

a) CD: Minimum 50% decrease in the Two-Point Patient-Reported Outcomes (PRO2) score (stool frequency and abdominal pain).
b) UC: Minimum 50% decrease in the PRO2 score (stool frequency and rectal bleeding).

Quality of evidence: High; Grade: High

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

Because of the strong correlation of PROs with patient well-being, this target should be assessed early and frequently throughout the disease course. The PRO has become increasingly important in determining treatment response both in clinical practice and clinical trials. The PRO2 score [Table 6] was developed and validated for assessment of UC activity state. A PRO2 score of zero indicates inactive disease, and a score of 6 indicates severe disease with spontaneous bleeding.[104] The STRIDE II study reinforces a drop of a minimum of 50% in the PRO2 score for both UC and CD as a treatment target [Table 6].[92]

Statement 26: We recommend using clinical remission as an intermediate target of treatment in adults, which is defined as follows:

a) CD: PRO2 (stool frequency ≤3 and abdominal pain ≤1 and) or HBI <5.
b) UC: PRO2 (stool frequency = 0 and rectal bleeding = 0) or a partial Mayo score of <3 and no individual element score >1.

Quality of evidence: High; Grade: High

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

Table 6: PRO2 score questions for ulcerative colitis[92]

Question	Response
Please indicate how you perceive your stool frequency (based on the last 3 days)	Normal 1-2 more stools than normal 3-4 more stools than normal 5+ more stools than normal
Please indicate the severity of your rectal bleeding (based on the last 3 days)	No blood seen Streaks of blood seen with stools for half of the time Obvious blood with stool most of the time Blood alone passed (with no stool)

PRO2=Two-Point Patient-Reported Outcomes

We agree with the IOIBD consensus regarding the definition of clinical remission for adults and its consideration as an intermediate target of treatment.[92] This is based on the data from clinical trials that showed a statistically significant yield of using the PRO2 in patients with UC[105] and CD.[106] The effect estimates were similar for using a two-point and a three-point PRO.[106]

Statement 27: FC obtained within 12 weeks of starting medications in IBD patients may be used as an indicator for the biochemical response.

Quality of evidence: Moderate; Grade: Moderate.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

FC was reported to have a predictive value of long-term outcome when measured 12 weeks after treatment initiation.[107] Elevated FC levels were found to have a probability of 53–83% of relapse during the next 2–3 months.[108] In other literature studies, FC levels measured 12–14 weeks after anti-tumor necrosis factor (anti-TNF) initiation were found to be predictive of clinical remission.[109,110]

Statement 28: Cross-sectional imaging obtained 6–9 months from starting the treatment can be used to evaluate the transmural response to therapy in CD.

Quality of evidence: Moderate; Grade: Moderate.

Strength of recommendation: Very strongly recommended (90% of panel strongly agreed).

Cross-sectional imaging represented by IUS, CT, or MRI can be used to evaluate the transmural response to therapy in CD. In a prospective multicentric longitudinal study of patients with active CD, all patients underwent clinical assessment and sonographic examination at baseline, 12 weeks after treatment initiation, and after 1 year of treatment, and the authors concluded that sonographic response after 12 weeks of therapy predicts 1-year sonographic response (i.e., 96.5% of patients with sonographic improvement at 52 weeks had a clinical remission).[111] Another multicentric trial evaluated the role of IUS for monitoring treatment response, and the authors found that all sonographic parameters determined during IUS showed a significant response to treatment.[112] These parameters included bowel wall thickness, vascularization parameters, and fibro-fatty proliferation.[112]

The value of CT was assessed in a retrospective study on infliximab-treated patients with CD.[113] A poor-to-fair correlation was found between CT enterography features of response, improved clinical symptoms or endoscopic appearance, and reduction of CRP (κ =0.26, 0.07, and 0.30, respectively).[113] The authors also concluded that only the "comb sign" on the index CT enterography was predictive of radiological response.[113]

Even though CT might be a suitable method to determine disease activity in CD, it should not be used for monitoring disease activity if MRI or IUS is available, because of radiation concerns. A prospective single-center trial that evaluated patients with CD treated with anti-TNF (infliximab or adalimumab) indicated that the Magnetic Resonance Index of Activity (MaRIA) score significantly changed at week 26 and that the overall MaRIA score correlated well with endoscopic score, both at baseline and at week 26.[114] The authors concluded that the MaRIA has high accuracy (sensitivity of 93% and specificity of 77%) for the prediction of endoscopic MH. Accordingly, it can be considered as a reliable monitoring indicator of TNF antagonists in CD.[114]

Statement 29: Endoscopic reassessment in UC and CD should be performed in cases of relapse, prolonged disease activity, new unexplained symptoms, and before switching between advanced therapeutic agents.

Quality of evidence: Moderate; Grade: Moderate.

Strength of recommendation: Very strongly recommended (90% of panel strongly agreed).

Endoscopy remains the reference standard for follow-up of active disease in UC and CD, and several studies determined the benefit of MH outlined through endoscopy in patients with UC and CD. MH was reported in a recent meta-analysis to have an odds ratio (OR) of 4.5 for achieving clinical remission at ≥52 weeks.[115] The ORs for achieving long-term MH, sustaining long-term corticosteroid-free remission, and remaining free of colectomy were 8.4, 9.7, and 4.15, respectively.[115]

In a prospective multicenter cohort study, the authors showed that endoscopy was the most sensitive method to detect the earliest mucosal changes (OR 0.52, 95% CI 0.277–0.974) and that severe endoscopic recurrence at 1 year seems to predict a clinical relapse.[116]

Statement 30: EH is defined as follows:
(a) CD: no ulceration or an SES-CD score less than 3 points (e.g., SES-CD ulceration subscore equal zero).
(b) UC: Ulcerative colitis endoscopic index of severity score up to one point or Mayo endoscopic subscore equal to zero.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

We agree with the STRIDE II recommendation regarding the measurement of EH.[92] The STRIDE II guidelines recommend measuring the EH in CD by an SES-CD score of less than 3 points or absence of ulcers.[92] In UC, the guidelines recommend measuring the EH by 1 or less points on the UCEIS or 0 points on Mayo endoscopic subscore.[92]

Statement 31: EH should be evaluated within 3–6 months in UC and 6–9 months in CD following treatment initiation in individuals with IBD, who have clinically responded to medical therapy.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (90% of panel strongly agreed).

The use of EH as an endpoint for both UC and CD treatment is appealing based on the consistent findings from the literature showing that when EH occurs, there was a low probability of disease flare or need for hospitalization and/or surgery.[117] The time to EH assessment is based on the approximate reported time of healing with different therapies, which range from 6 to 14 months in CD and from 2 weeks to 12 months in UC.[117]

Statement 32: Histologic remission and transmural healing are not recommended treatment goals in CD or UC. However, in UC, documentation of histologic remission using the Robarts Histopathological Index of severity (RHI) or the Nancy Index (NI) can be used in addition to endoscopic remission, as its presence reflects a deeper degree of healing. In CD, transmural healing (as measured by CTE, MRE, or IUS) is also recommended as a supplement to EH.

Quality of evidence: Moderate; Grade: Moderate.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

The RHI and the NI are two scores with variable features designated to classify UC patients according to their degree of healing.[118,119] The STRIDE II recommendations state that histologic remission and transmural healing are not recommended treatment goals in CD or UC.[92] The recommendations, nonetheless, justified the use of histological remission and/or transmural healing as an adjunct to endoscopic remission as an indicator of deeper healing levels.[92]

Statement 33: In UC and CD, normalization of quality of life related to health and absence of disability are considered long-term therapeutic goals.

Quality of evidence: Moderate; Grade: Moderate.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

For several decades, clinical remission, normalization of laboratory markers, and EH, have long been the mainstay endpoints for IBD treatment. Recently, however, the concept of health-related quality of life has been incorporated into the therapeutic plan of many disorders, including IBD.[120] This concept refers to measuring the impact of the disease on the patients' quality of life and having a normalized quality of life as a therapeutic target during disease treatment. This outcome measure has been incorporated into many clinical trials where normalization of the quality of life was defined as restoring normal scores on quality-of-life questionnaires, such as the 36-item Inflammatory Bowel Disease Questionnaire.[121]

Statement 34: Before starting any biologic therapy, including anti-TNF treatment, patients with IBD must be screened for latent TB using chest radiography and a purified protein derivative (PPD) skin test and/or an IGRA.

Quality of evidence: High; Grade: High

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

Active TB is an absolute contraindication for biologic therapy.[122] Reactivation of TB is a potential adverse event when using anti-TNF agents. Therefore, latent TB must be excluded before biologic treatment initiation using a standard diagnosis protocol that includes chest radiography and a PPD skin test and/or an IGRA test. Anti-TNF agents were reported to have an almost 14-fold increased risk of TB infection or activation compared to their counterparts

from the healthy population.[123] Given the significantly high incidence of TB in Saudi Arabia (14–17 cases per 100,000 population),[124] it is crucial to test for latent TB before initiating anti-TNF in the country.

Statement 35: Biologic therapies should be used in conjunction with preventive anti-TB therapy in IBD patients with confirmed latent TB infection. Biologic therapy can be initiated 4 weeks after starting anti-TB regimens.

Quality of evidence: High; Grade: High

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

If latent TB infection is confirmed, preventive anti-TB therapy should be immediately started and continued for 3–6 months depending on the regimen used.[122] Biologic therapy can be safely started 4 weeks after starting preventative anti-TB therapy. Treating latent TB was found to be effective in conjunction with biologics for patients with IBD.[125] The risk of reactivation, however, was not eliminated.[125] In a study of 35 patients with TB comorbid with IBD, treatment with isoniazid was found to be effective in patients with IBD treated with infliximab, adalimumab, certolizumab pegol, and vedolizumab.[125] In this study, the risk of TB reactivation was 0.52%.[126] Recent recommendations for latent TB treatment propose combination therapies, such as combined daily doses of Isoniazid and rifapentine for 12 weeks, isoniazid and rifampicin for 12 weeks, or daily rifampin only for 4 months.[127]

Statement 36: A comprehensive risk assessment of CD patients at baseline should be considered, and the preferred treatment strategy should be based on the risk profile. A "step-up" approach is recommended for patients who do not have high-risk features. A "top-down" approach is recommended for patients with high-risk features.

Quality of evidence: High; Grade: High

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

The term "step-up" refers to a sequential treatment strategy that often begins with a less effective, potentially less toxic treatment strategy, such as budesonide, with escalation to the highly effective, but potentially more toxic treatment options, such as prednisone, immunosuppressants, and biologic therapy, in patients who failed each line of therapy.[128] This approach should be offered to patients without high-risk features or poor prognostic markers, such as age at onset <40 years, smokers, extraintestinal manifestations at early disease, perianal disease at diagnosis, stenotic or penetrating disease behavior, elevated CRP, severe endoscopic lesions, and the early need for corticosteroids.[129,130] Cachexia, fever, dehydration, sepsis, complex perianal disease, abscess, palpable masses, signs of peritoneal irritation, severe anemia, hypoalbuminemia, and electrolyte disturbance are also poor prognostic factors at early disease.[129]

In this treatment strategy, overtreatment should be avoided. Exposure to medications and the risk of developing adverse events should be avoided, particularly in patients who perform adequately well with the standard treatment strategies. Similarly, many physicians are reluctant to provide appropriate advanced therapies because of the concern of potential toxicity in patients with uncontrolled inflammation and inadequate treatment response on standard paradigms.[131]

The idea of using highly effective but potentially more expensive treatment strategies early in the course of a chronic illness to prevent disease progression and disability has gained popularity for the treatment of patients with CD. Furthermore, the "top-down" strategy, suggested by D'Haens *et al*.,[132] appears to have promising results for the treatment of CD.[133] This is particularly important given the high prevalence of CD with high-risk features, in Saudi Arabia.[2]

Statement 37: The conventional "step-up" approach is the core approach for the treatment of UC, except for patients who present with acute severe ulcerative colitis (ASUC) that requires hospitalization.

Quality of evidence: High; Grade: High

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

The "step-up" approach is favored in UC, but careful monitoring of clinical symptoms, biomarkers, and endoscopy is still warranted, and escalation to advanced therapies should be performed when remission is not achieved.[134] This, however, should not be the case when managing cases of ASUC.[135-137] The treatment of ASUC is complex and requires multidisciplinary inpatient care. Recent data favor the "top-down approach" using rescue therapy as an initial medical treatment, but its failure mandates surgical intervention.[135-137]

Treatment of luminal CD

Statement 38: We recommend "against" using 5-ASA for the induction or maintenance of remission in CD.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

A meta-analysis conducted by the ECCO team in 2019 included seven eligible RCTs that compared the use of oral 5-ASA or sulfasalazine with placebo in patients with active CD.[7] Overall, there was no significant effect for induction of clinical remission, and among the five trials of 5-ASA alone, there was also no benefit over placebo for inducing clinical remission.[138]

Statement 39: Oral budesonide should only be used to induce clinical remission in individuals with active mild-to-moderate CD, confined to the terminal ileum and/or right colon.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

A Cochrane systematic review and meta-analysis that included 25 RCTs that compared budesonide at a dose of 9 mg/day with placebo, indicated that budesonide was superior to placebo for inducing clinical response (OR: 2.93; 95% credible interval (CrI)), and clinical remission (OR: 1.69; CrI, 1.05–2.75) in patients with mildly active CD in the small and/or large intestine, limited to the ascending colon.[126]

In another Cochrane systematic review and meta-analysis that compared budesonide at a dose of 9 mg/day with mesalazine up to 4.5 g/day, budesonide was not superior to mesalazine for inducing clinical remission in patients with mildly active CD in the small and/or large intestine, but the clinical response was more frequently seen in patients receiving budesonide (OR 1.27; 1.03–1.56), which exhibited a good safety profile.[139]

Statement 40: Systemic corticosteroids can be used for the induction of remission in active, moderate-to-severe CD.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (90% of panel strongly agreed).

A Cochrane systematic review evaluated data from two RCTs regarding the efficacy of systemic corticosteroids (oral prednisolone or oral methylprednisolone) compared with placebo, for the treatment of moderate-to-severely active CD. The results indicated that the clinical response was more common in patients receiving methylprednisolone than in patients receiving placebo, and corticosteroids were reported to be twice as effective in inducing clinical remission than placebo.[140]

Statement 41: We recommend "against" using thiopurines monotherapy for the induction of remission in moderate-to-severe CD. We recommend using thiopurines or parenteral methotrexate as corticosteroid-sparing agents for maintenance of remission in patients who are corticosteroid dependent.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (80% of panel strongly agreed).

The pooled analysis of several studies failed to show any superior effect of thiopurines to placebo in inducing remission in CD.[7] As the quality of evidence about the role of thiopurines in inducing remission is low in moderate-to-severe CD,[7] we recommend against its use for this purpose.

Statement 42: We recommend Anti-TNF therapies for induction and maintenance of remission in patients with moderate-to-severe CD who failed conventional therapy.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (90% of panel strongly agreed).

Anti-TNF agents can be used in patients with CD who fail conventional therapies, such as systemic or topical corticosteroids and immunosuppressants such as azathioprine.[141] Anti-TNF therapies are fast-acting monoclonal antibodies directed against TNF-α. Approved anti-TNF therapies for CD include adalimumab, infliximab, and certolizumab pegol.

Infliximab is a chimeric mouse–human immunoglobulin [Ig] G1 monoclonal antibody, administered intravenously at a dose of 5 mg/kg at 0, 2, and 6 weeks during induction and at every 8 weeks thereafter. Adalimumab

is a fully humanized IgG1 monoclonal antibody given subcutaneously (SC) at a dose of 160 mg, and then 80 mg 2 weeks after induction, followed by 40 mg SC every 2 weeks. Certolizumab pegol is a PEGylated Fab fragment against TNF-α, self-administered SC at a dose of 400 mg at weeks 0, 2, and 4, followed by 400 mg every 4 weeks thereafter.[142-144]

Results from several metanalyses of RCTs demonstrated superiority of anti-TNF agents (infliximab, adalimumab, and certolizumab pegol) over placebo, considering their efficacy in inducing clinical remission and clinical response.

The choice of anti-TNF agent depends on patient preference, availability, cost, and accessibility.[145] However, infliximab combined with azathioprine (AZA) and adalimumab monotherapy were reported to be superior to certolizumab pegol for induction of remission.[146]

Statement 43: We recommend using adalimumab monotherapy rather than in combination with an immunosuppressant for induction of clinical remission and response in biologic naïve CD patients.

Quality of evidence: Moderate; Grade: Moderate.

Strength of recommendation: Very strongly recommended (90% of panel strongly agreed).

The use of adalimumab and thiopurine combination therapy was compared to the use of adalimumab monotherapy in the induction of clinical remission in drug-naïve CD patients in one study.[145] The results revealed non-superiority of the combination therapy with adalimumab to monotherapy, regarding inducing clinical remission.[145] The remission rates at week 26 were 71.8% and 68.1% in the monotherapy and combination therapy groups, respectively ($P = 0.63$).[145] Furthermore, the discontinuation rate among patients receiving combination therapy was significantly higher than in patients receiving monotherapy (16.5% vs. 1.2%, respectively), because of the adverse events and poor safety profile.[145]

Evidence also exists for using adalimumab monotherapy as a second-line treatment for CD.[147,148] Data from a prospective study on 44 patients in a single center in England showed that the use of adalimumab as a second-line monotherapy, following infliximab failure, resulted in a 77% initial response rate (defined as a two-point reduction in HBI).[147] Sustained clinical benefit was achieved in 64% of the patients.[147]

Statement 44: We recommend using thiopurines in combination with infliximab for induction of remission in patients with moderate-to-severe CD who failed conventional therapy.

Quality of evidence: Moderate; Grade: Moderate.

Strength of recommendation: Very strongly recommended (90% of panel strongly agreed).

The Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease (SONIC) study compared the efficacy of infliximab combined with AZA over infliximab monotherapy in patients naïve to both therapies, who failed to respond to steroids or 5-ASA.[149] Combination therapy resulted in higher rates of clinical remission at week 26 compared with infliximab monotherapy (56.8% vs. 44.4%, respectively) and was also more likely to result in MH (43.9% vs. 30.1%, respectively).[149]

Statement 45: For moderate-to-severe CD patients who failed conventional therapy, we recommend ustekinumab to induce remission.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (90% of panel strongly agreed).

Ustekinumab is an IgG1 monoclonal antibody used for the treatment of CD. It acts via binding to the p40 subunits of inflammatory interleukins 12 and 23.[150] It is administered as an IV weight-based infusion induction at 6 mg/kg, followed by 90 mg SC every 8-12 weeks for maintenance of remission.[151]

The efficacy of ustekinumab in the induction of clinical remission in patients with moderate-to-severe active luminal CD was analyzed by a systematic review and meta-analysis of RCTs that compared ustekinumab to placebo.[152] Pooled results showed 16% of patients receiving ustekinumab achieved clinical remission at week 6 compared to 10% of patients receiving placebo (RR 0.92, 95% CI: 0.88–0.96).[152] These results were obtained from three studies with high-quality evidence.[152] The clinical remission rate in the subgroup of patients who received a 6 mg/kg dose was 45% compared to 29% among patients receiving placebo (RR 0.78, 95% CI: 0.71–0.85, moderate-quality evidence, three studies).[152]

Statement 46: For moderate-to-severe CD patients who failed conventional therapy, vedolizumab is proposed to induce remission

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

Vedolizumab is another monoclonal IgG1 antibody used for the treatment of CD. It is a gut-selective agent with anti-inflammatory activity via blocking the α4β7 integrin.[153] It is administered as an IV infusion at a fixed dose of 300 mg at 0, 2, and 6 weeks for induction and at every 8 weeks thereafter for maintenance.

Several RCTs evaluated the treatment with vedolizumab or placebo and reported on induction of clinical response and clinical remission in adult patients with moderate-to-severe active CD.[153-154] In all these studies, patients treated with vedolizumab had significantly higher clinical remission rates and clinical response. In the EVOLVE trial, patients who received vedolizumab had a significantly lower incidence of disease exacerbation (HR 0.58, CI 0.45–0.76), lower incidence of adverse events (HR 0.40, CI 0.19–0.85), and similar clinical effectiveness (HR 0.42, CI 0.28–0.62) than other anti TNFα.[155] In the VICTORY consortium data, vedolizumab was reported to achieve clinical remission in 51% of the patients, endoscopic remission in 41%, corticosteroid-free remission in 37%, and deep remission in 30% of the patients, at 12 months.[156] In the prospective phase 3b VERSIFY clinical trial, treatment with vedolizumab was found to be efficacious in inducing endoscopic, radiological, and histological remission in patients with moderate to severely active CD.[157] Endoscopic remission was achieved in 11.9% (95% CI 6.3–9.8) and 17.9% (95% CI 8.9–30.4) of patients at week 26 and week 52, respectively.[157] Radiological remission (evaluated by MRE) was achieved in 21.9% (95% CI 3.9–40.0) and 38.1% (95% CI 18.1–61.6) of patients at week 26 and week 52, respectively.[157] Histologic remission was seen in 24.4% (95% CI 15.3–35.4) and 28.3% (95% CI 17.5–41.4%) of patients at week 26 and week 52, respectively.[157]

Statement 47: For moderate-to-severe CD patients who failed anti-TNF therapy, we recommend using either ustekinumab or vedolizumab; selection should be based on a personalized medical approach.

Quality of evidence: High; Grade: High.

Strength of recommendation: Strongly recommended (50% of panel strongly agreed).

In a systematic review and meta-analysis, the efficacy of ustekinumab was indirectly compared to the efficacy of vedolizumab in inducing remission in patients with moderate-to-severe active luminal CD, who were non-responsive or intolerant to previous anti-TNF agents.[158] The authors reported no significantly different clinical response (relative benefit [RB]: 1.14; 95% CI: 0.65–1.99; $P = 0.64$) and clinical remission rates (RB: 1.16; 95% CI: 0.54–2.48; $P = 0.71$), although the quality of data was low.[158]

Ustekinumab was reported to be more effective than vedolizumab on long-term basis.[159] In a systematic review and meta-analysis of 1,026 patients with CD, ustekinumab and vedolizumab showed comparable clinical (OR 1.36, 95% CI: 0.74–2.47), steroid-free (OR 1.24, 95% CI: 0.79–1.92), and biological (OR 0.80, 95% CI: 0.50–1.28) remission rates at week 14.[159] However, ustekinumab was superior to vedolizumab in achieving clinical (OR 1.87, 95% CI: 1.18–2.98), steroid-free (OR 1.56; 95% CI: 1.23–1.97), and biological (OR 1.86; 95% CI: 1.03–3.37) remission at week 52.[159]

Treatment of perianal fistulizing CD

Statement 48: Infliximab is recommended as the first choice of biologic to induce and maintain remission in complex perianal fistulae in CD.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

Infliximab was the first agent shown to be effective in an RCT for inducing the closure of perianal fistulae and maintaining this response for more than 1 year.[160] Present *et al*.,[160] in their study of 94 patients with CD complicated with fistulas, in 1999, reported that ≥50% reduction in the number of draining fistulae was achieved in 68%, 56%, and 26% in patients who received infliximab 10 mg/kg, infliximab 5 mg/kg, and placebo, respectively ($P = 0.002$). Fistula's closure was achieved in 55%, 38%, and 13% in the three groups, respectively ($P < 0.05$).

In a meta-analysis of the existing data, infliximab was found to be effective in inducing fistula healing (RR: 3.57; 95% CI: 1.38–9.25) and in maintaining clinical fistula healing (RR: 1.79; 95% CI: 1.10–2.92), with no significant risk of serious adverse effects compared with placebo.[7] In clinical practice, infliximab is often used in combination with immunosuppressants, antibiotics, and surgical treatment.[161]

Statement 49: Adalimumab can be used to induce and maintain remission in complex perianal fistulae in CD.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

A meta-analysis of the current data showed that adalimumab was superior to placebo (RR: 2.57; 95% CI: 1.13–5.84) for fistula healing after 56 weeks.[7] Furthermore, the open-label CHOICE trial showed that complete fistula healing also could be achieved in patients who failed on infliximab. After a washout of ≥8 weeks, initiating adalimumab achieved complete healing of the fistulas in 39% of patients, after infliximab failure.[162]

Statement 50: A combined medical and surgical approach is recommended for patients with CD and complex perianal fistula.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

Further research is needed to reduce uncertainty, but it is reasonable to accept a multidisciplinary approach incorporating medical and surgical treatment for complex perianal fistula in patients with CD. Some data in the literature support the use of combined medical and surgical approach. In PISA I trial, 44 patients with perianal CD fistula were randomized to a 1-year chronic seton drainage (group I), a 1-year anti-TNF therapy (group II), or surgical closure after 2 months with a short anti-TNF course.[163] Seton drainage was inferior to the other two treatment modalities with the highest re-intervention rate (66, 40, and 21.43%, respectively; $P = 0.02$), and group I was terminated early because of the safety data.[163] The two other treatment modalities were comparable.[163] Closely similar results were observed in PISA II trial that included groups II and III who participated in PISA I[164] After a follow-up of approximately 5 years, the two groups had comparable clinical closure rates ($P = 0.533$), recurrence rate ($P = 0.111$), and incontinence rates. Radiological activity, however, was encountered more in group III ($P = 0.018$).[164]

A study of 22 patients with fistulizing anal CD, who received infliximab and surgical intervention (in the form of drainage, seton suture insertion, defunctioning, or proctectomy), showed that the combined medical-surgical approach was safe and effective on short-term basis.[165] Another single-center retrospective chart review study of 29 patients with fistulizing anorectal CD showed that combined seton placement, infliximab infusion, and maintenance therapy, resulted in complete healing of the fistula in 67% and partial healing in 19% of the patients.[166] A comparative study between 23 patients who received infliximab only and nine patients who received combined infliximab and surgical therapy (i.e., examination under anesthesia with seton placement) revealed a favorable initial response of combined therapy (100% vs. 82.6%, $P = 0.014$), longer duration to fistula recurrence (13.5 months vs. 3.6 months, $P < 0.001$), and lower rate of recurrence (44% vs. 79%, $P < 0.001$).[167]

Statement 51: We recommend "against" using antibiotics alone for the closure of fistulae in CD patients with complex perianal fistulae.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (90% of panel strongly agreed).

Antibiotics are widely used in the treatment of perianal CD, but most published studies are uncontrolled.[168] Despite the lack of evidence to support their role as monotherapy in closing perianal fistulae, antibiotics remain indicated and recommended to treat and control perianal sepsis.

Treatment of UC

Statement 52: Oral and/or topical 5-ASA derivatives are recommended as first-line treatment for the induction and maintenance of remission in mild-to-moderate UC.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

Oral 5-ASA is considered as the standard treatment for mild-to-moderately active UC. Data from a meta-analysis showed a positive effect of oral 5-ASA for the induction of remission in mild-to-moderately active UC.[143,169] A meta-analysis of 11 RCTs showed that the number needed to treat was only six for 5-ASA to induce remission in

UC.[143,169] Higher doses of 5-ASA were reported to be more efficacious than lower doses.[143,169] The RR of administering a dose of ≥2.0 g/day was 0.79 (95% CI 0.64–0.97) in comparison to a dose of less than 2 g/day.[143,169] Once-daily dosing was reported to have the same effectiveness as divided doses.[170] A dose of 4 g/day was reported to be safe and effective for the induction of remission and MH, followed by a maintenance dose of 1.5–2.25 g/day.[171]

Statement 53: Budesonide MMX topical and/or systemic corticosteroids are recommended for induction of remission in UC, in patients who failed to respond to mesalazine derivatives.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

RCT have shown that oral budesonide MMX 9 mg daily was significantly more effective than placebo, and could induce remission in mild-to-moderate UC, being as effective as 5-ASA.[172,173] In a double-blinded prospective RCT conducted on 36 patients, the use of budesonide MMX 9 mg tablet resulted in remission and/or ≥50% reduction in colitis activity index in 47.1% of patients at 4 weeks, in comparison to 33.3% with placebo.[172] Similarly, the CORE I trial results showed remission rates of 17.9%, 13.2%, and 12.1% among patients who received 9 mg of budesonide, 6 mg of budesonide, and placebo, respectively.[174] In the CORE II trial, the combined clinical and endoscopic remission rates were 17.4%, 8.3%, 12.6%, and 4.5% for budesonide MMX 9 mg, budesonide MMX 6 mg, budesonide controlled ileal-release capsules 9 mg, and placebo, respectively.[173] In patients inadequately controlled on 5-ASA, budesonide MMX was found to achieve a combined clinical and endoscopic remission in 13% of the patients versus 7.5% in patients who received placebo ($P = 0.048$).[175] Budesonide MMX, however, has a limited efficacy in patients with extensive CD.[173,174]

Other than budesonide MMX, systemic steroids and/or topical steroids were reported to be effective in patients with UC, who fail on 5-ASA derivatives.[176,177] Corticosteroids were superior to placebo and 5-ASA in inducing remission in patients with active UC.[176,178] Oral conventional steroids at a dose of 0.75–1 mg/kg/day oral prednisolone-equivalent should be considered in patients who fail on budesonide MMX.[176] Topical steroids should be considered in patients with inadequate response to 5-ASA. They can be used alone in patients with isolated proctitis.[49]

Statement 54: Oral budesonide MMX is recommended over conventional oral corticosteroids to induce remission in UC. If conventional oral corticosteroids are used, the patient should be advised about common and serious side effects of corticosteroids.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

Oral corticosteroids are very effective when used as induction agents, mainly to control symptoms. However, the use of corticosteroids is limited by significant safety concerns. Side effects of systemic corticosteroids, such as the increased risk of infection, weight gain, acne, glucose intolerance, hypertension, glaucoma, and sleep/psychological disturbances, should be considered and relayed to the patient. Furthermore, corticosteroids should never be used as maintenance agents as their prolonged use is associated with metabolic bone disease, cataract formation, adrenal insufficiency, risk of opportunistic infections, diabetes mellitus, and hypertension. Budesonide MMX may be considered as an alternative to conventional corticosteroids in patients with mild-to-moderate UC and failure of response to 5-ASA therapy.[179] In a 9-week prospective double-blinded RCT conducted on 72 patients with mild-to-moderately active UC, the use of budesonide was associated with fewer adverse events (14.7%) than the use of oral prednisolone (18.4%). Furthermore, cortisol suppression and reduction in bone mineral density were seen in patients who received prednisolone but not budesonide.[180]

Statement 55: We recommend using thiopurines to maintain remission in patients with UC who are corticosteroid resistant or corticosteroid dependent.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

Numerous studies confirm a benefit of thiopurines over placebo for maintaining steroid-induced remission in UC.[181,182] A recent Cochrane review included 232 patients from four maintenance studies of

azathioprine versus placebo and showed a benefit of azathioprine over placebo.[183] In a systematic analysis of seven RCTs, remission was achieved in 42% of patients receiving azathioprine, and in 63% of patients receiving sulfasalazine, with an OR of 1.52 (95% CI 0.66–3.50).[183]

Statement 56: We recommend using vedolizumab over adalimumab to induce remission in moderate-to-severe ambulatory UC patients naïve to biologic agents.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

The VARSITY trial was designated to evaluate the effect of IV vedolizumab (administered as 300 mg at weeks 0, 2, and 6 then every 8 weeks thereafter) versus subcutaneous adalimumab (administered as 160 mg at week 0, 80 mg at week 2, and 40 mg fortnightly thereafter) in patients with moderate to severely active UC, who had failed conventional therapies.[184] Data from this study showed that clinical remission at week 52 was achieved in 31.3% of patients who received vedolizumab versus 22.5% in patients who received adalimumab ($P = 0.0006$). MH was achieved in 39.7% and 27.7% of the two groups, respectively ($P = 0.0005$), and corticosteroid-free remission was comparable between the two groups.[184] These data provide support for vedolizumab as a first-line biologic option for UC failing conventional therapy (i.e., 5-ASA, corticosteroids, azathioprine/6-mercaptopurine, and anti-TNF).[185]

Statement 57: We recommend using in patients with moderately active UC who have failed conventional therapy, treatment with biological therapies, i.e., infliximab, golimumab, adalimumab, vedolizumab, or ustekinumab, is recommended.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

All the agents mentioned above could be used to treat patients with moderately active UC who have failed conventional therapy. Still, the choice of drug should be determined by clinical factors, patient choice, cost, likely adherence, and local infusion capacity.[186-188]

Statement 58: We recommend using ustekinumab for induction and maintenance of remission in patients with moderate-to-severely active UC.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

The UNIFI trial investigated ustekinumab as an induction and maintenance therapy in adults with moderate-to-severely active UC, who did not respond to or did not tolerate standard therapies, such as corticosteroids, immunosuppressants, ≥1 anti-TNF therapies, and vedolizumab.[189] Patients were randomized 1:1:1 to receive a single IV dose of placebo, 130 mg ustekinumab, or approximately 6 mg/kg ustekinumab. Both active treatment groups achieved significantly higher rates of clinical remission, EH, and clinical response at week 8 compared to placebo.[189] Clinical remission at week 44 was achieved in 43.8%, 38.4%, and 24.0% among patients receiving ustekinumab every 8 weeks, patients receiving ustekinumab every 12 weeks, and patients receiving placebo, respectively ($P < 0.001$).[189] Clinical response was maintained among 71%, 68%, and 44.6% of the three groups, respectively.[190] EH was seen in 51.1%, 43.6%, and 28.6% of the three groups, respectively.[189]

Statement 59: We recommend using ozanimod for induction and maintenance of remission in UC following failure of conventional and/or advanced therapies.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

The TRUE NORTH phase 3 multicenter double-blinded RCT investigated ozanimod, a selective sphingosine-1-phosphate receptor modulator, as an induction and maintenance therapy in adults with moderate to severely active UC.[190] Two cohorts of patients were recruited. Patients in cohort 1 were randomized to receive 1 mg of ozanimod hydrochloride or placebo once daily, in the 10-week induction period.[190] In cohort 2, patients received open-label ozanimod hydrochloride 1 mg daily.[190] At week 10, patients who responded clinically to ozanimod were randomized again to receive ozanimod or placebo as maintenance therapy from week 10 to week 52.[190] At week 10, clinical remission was achieved in 18.4% of patients who received ozanimod and 6% in those who received

placebo during the induction period ($P < 0.001$).[190] Clinical response was maintained in 37% of patients who continued to receive ozanimod and in 18.5% of patients who received placebo during the maintenance therapy period ($P < 0.001$).[190]

In the phase 2 TOUCHSTONE open-label extension (OLE) clinical trial, patients who received ozanimod or placebo in the double-blinded period of the TOUCHSTONE trial were followed up for ≥4 years to investigate the long-term safety and efficacy of ozanimod, in moderate to severely active UC.[191] Clinical response was maintained in 93.3% of patients at OLE week 200, and remission was maintained in 82.7% using observed analysis.[191] The clinical response and remission rates were 41% and 37%, respectively, when non-responder imputation analysis was used.[191] Histological remission was achieved in 46.3% of patients at week 56 and 38.5% in patients at week 104.[191] Endoscopic improvement was seen in 46.4% of patients at week 56 and 46.5% at week 104.[191]

Statement 60: We recommend using upadacitinib for induction and maintenance of remission in UC following failure of conventional and/or advanced therapies.

Quality of evidence: High; GRADE: High.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

Two trials, the U-ACCOMPLISH and the U-ACHIEVE phase 3 clinical trials, investigated the efficacy of upadacitinib, a selective and reversible Janus kinase inhibitor, as an induction and maintenance therapy for adult patients with moderate-to-severely active UC.[192-195]

In the U-ACCOMPLISH trial,[192,193] adult patients with moderate-to-severely active UC who failed response to conventional therapy (i.e., corticosteroids, aminosalicylates, immunosuppressants, and/or biologics) were randomized 2:1 to receive upadicitinib 45 mg or placebo for 8 weeks. Clinical remission was achieved in 33.5% of patients receiving upadicitinib versus 4.1% of those receiving placebo.[192] Symptomatic improvement and EH occurred in 74.5% and 44% of patients receiving upadicitinib versus 25.4% and 8.3% of those receiving placebo.[192]

In the U-ACHIEVE phase 2b trial,[193] adult patients with moderate to severely active UC, with inadequate response to conventional therapy (i.e., corticosteroids, immunosuppressants, and/or biologics), were randomized to receive upadacitinib (7.5, 15, 30, or 45 mg) or placebo daily for 8 weeks.[193] Clinical remission was achieved in 8.5% ($P = 0.052$), 14.3%, ($P = 0.013$), 13.5% ($P = 0.011$), and 19.6% ($P = .0002$) of patients receiving 7.5, 15, 30, or 45 mg upadacitinib, respectively, in comparison to none of those receiving placebo.[193] Endoscopic improvement occurred in 14.9% ($P = 0.033$), 30.6% ($P < 0.001$), 26.9% ($P < 0.001$), and 35.7% ($P < 0.001$) in comparison to 2.2% of those receiving placebo.[193] In U-ACHIEVE phase 3 clinical trial,[195] adult patients with moderate-to-severely active UC were randomized 2:1 to receive upadacitinib or placebo for 8 weeks. Clinical remission was achieved in 26.1% of patients receiving upadacitinib versus 4.8% of those receiving placebo ($P < 0.001$).[195] Endoscopic improvement occurred in 36.3% versus 7.4% ($P < 0.001$), endoscopic remission occurred in 13.7% versus 1.3% ($P < 0.001$), and clinical response was seen in 60. 1% versus 27.3% ($P < 0.001$) of patients receiving upadacitinib versus placebo, respectively.[195]

Statement 61: We recommend using tofacitinib as a second-line treatment in adult outpatients with moderate-to-severe UC who failed biologic agents.

Quality of evidence: High; Grade: High.

Strength of recommendation: Strongly recommended (60% of panel strongly agreed).

A recent meta-analysis evaluated tofacitinib as a treatment option of moderate-to-severely active UC among various biologic agents, and the results showed superior induction rates of clinical remission.[196] In this meta-analysis, infliximab had the highest potency to induce remission and endoscopic improvement in biologic-naive patients with an OR of 4.07 versus placebo (95% CI, 2.67–6.21: surface under the cumulative ranking curve [SUCRA], 0.95).[196] Three phase III double-blinded RCTs were conducted to evaluate the effect of tofacitinib in adults with UC, i.e., OCTAVE 1, OCTAVE 2, and OCTAVE sustain trials.[197] In OCTAVE 1 and 2, patients with moderate-to-severely active UC, who failed on conventional or anti-TNF therapies, were recruited to receive tofacitinib induction (10 mg twice daily for 8 weeks) or a placebo. In OCTAVE sustain, the patients who responded to induction therapy were assigned to receive either maintenance therapy (5–10 mg twice daily) or a placebo. Results from the three OCTAVE

trials showed that remission was achieved in 18.5% and 8.2% of the patients who received tofacitinib and the patients who received placebo, respectively ($P = 0.007$) in the OCTAVE 1 trial, 16.6% and 3.6% in the two groups, respectively ($P < 0.001$) in OCTAVE 2, and 34.3%, 40.6%, and 11.1% in patients who received tofacitinib 5 mg, tofacitinib 10 mg, and placebo, respectively ($P < 0.001$) in OCTAVE sustain.[197]

Statement 62: We do "not" recommend using tofacitinib for patients with a history of thromboembolic disease, cardiovascular disease, or those ≥50 years old, with at least one cardiovascular risk factor, because of an increased risk of thromboembolic events.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

Recent data from an open-label study of rheumatoid arthritis patients (more than 50 years with at least one cardiovascular risk factor), comparing tofacitinib 5 mg or 10 mg twice daily with TNF inhibitor therapy, have shown a five-fold increase in pulmonary embolus for the group on 10 mg twice daily tofacitinib compared with TNF inhibitor therapy.[198] It is advisable that the high dose should not be used in patients at increased risk of pulmonary embolus. This increased risk has not been observed in studies conducted in UC. Considering these findings, the European Medicines Agency has released a black box warning concerning the risk of venous thromboembolism (VTE) associated with the use of tofacitinib, and recommended using tofacitinib at the lowest efficacious dose, and avoiding tofacitinib 10 mg twice daily as a maintenance treatment for patients with known VTE risk factors.[199]

In contrary, data from other studies showed no increased risk of major adverse cardiovascular events (MACE) or VTE with the use of tofacitinib.[200,201] The incidence rates of MACE and VTE in the pooled results of phase 3 OCTAVE two induction studies, the phase 3 OCTAVE Sustain maintenance study and the dose-escalation subpopulation of the long-term OLE OCTAVE open study, were 0.00 (0.00–5.38) and 0.00 (0.00–5.38), respectively.[202] Similarly, in the 7-year post label extension of the OCTAVE clinical trial, tofacitinib was demonstrated to have a consistent safety and an overall incidence rate of 0.16 (0.04–0.42) for MACE and 0.04 (0.00–0.23) for VTE.[203] Overall, we reiterate the previous comments that given the available efficacy data, from clinical trials conducted in UC, tofacitinib is considered as a treatment option for patients with moderate-to-severely active UC, even in patients with prior anti-TNF exposure. However, the risks and benefits of treatment must be considered for each patient individually.

Statement 63: We recommend "against" methotrexate use to initiate or maintain remission in adults with moderate-to-severe UC.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

A Cochrane review in 2015 that compared the use of methotrexate in the maintenance of remission of UC versus placebo, sulfasalazine, 6-mercaptopurine, and 5-ASA, failed to show a beneficial effect of methotrexate.[204] In comparison to the placebo, methotrexate maintained remission in 36% of the patients versus 54% among the placebo (RR 0.64, 95% CI 0.28 to 1.45).[204] Furthermore, a European double-blinded, randomized trial, compared 25 mg/week of parenteral methotrexate versus placebo. The results showed that methotrexate was not superior to placebo in achieving steroid-free remission at week 16.[205]

Statement 64: We recommend combining infliximab with thiopurines over infliximab monotherapy in moderate-to-severe UC. There is insufficient evidence to recommend combining other biologic therapies with thiopurines.

Quality of evidence: Moderate; Grade: Moderate.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

In the UC SUCCESS study, the efficacy of infliximab monotherapy, azathioprine monotherapy, and combination therapy was evaluated in 239 patients with moderate-to-severe UC.[206] At week 16, remission was achieved in 22.1%, 23.7%, and 39.7% in patients who received infliximab, azathioprine, and combination therapy, respectively ($P = 0.032$). MH was seen in 54.6%, 36.8%, and 62.8% of the three groups, respectively ($P = 0.001$). A recent technical review from AGA supports the combination of infliximab and thiopurines for the treatment of moderate-to-severe UC.[207] The relative risk

Statement 65: We recommend "against" 5-ASA continuation for maintenance of remission in adult ambulatory patients with moderate-to-severe UC who have attained remission with the use of immunosuppressants and/or biologic agents or tofacitinib.

Quality of evidence: Moderate; Grade: Moderate.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

of using thiopurines for achieving corticosteroid-free relapse was 1.25 (95%, CI 1.01–1.56) in comparison to placebo or 5-ASA in the UC-SUCCESS trial.[206] In a small RCT, infliximab could reduce the risk of colectomy in 45 patients with UC refractory to steroid treatment (RR, 0.44; 95% CI, 0.22–0.87).[207]

There is currently no strong evidence that supports the use of 5-ASA continuation for maintenance of remission in adult ambulatory patients with moderate-to-severe UC, who have attained remission with the use of immunosuppressants, biologic agents, or tofacitinib.[208,209] Several systematic reviews and meta-analyses demonstrated no added value for continuing 5-ASA in patients who achieved remission on biologics or AZA.[208,210] The continuation of 5-ASA along with biologics or tofacitinib was not found to be cost-effective in one study.[210]

Selection and sequencing of therapies in IBD

Statement 66: We recommend selecting biologic medications based on patient preferences, availability, cost, risk of infection, presence of extraintestinal manifestations of IBD, and the desired onset of response.

Quality of evidence: High; Grade: High.

Strength of recommendation: Strongly recommended (70% of panel strongly agreed).

Several studies have outlined the following factors as selection criteria for a biological agent selection: patient preferences, availability, cost, risk of infection, presence of extraintestinal manifestations of IBD, and the desired onset of response.[211-213] These criteria were based on the widely heterogenous patients' profiles (e.g., preference, risk of infection, and comorbidities), variable disease profiles (severity, state of activity, and the presence or absence of extraintestinal manifestations), and different drug profiles (e.g., cost, availability, and desired onset of action). An individualized treatment plan is suggested for each patient according to a combination of these three profile variables to optimize the treatment outcome.

Statement 67: We recommend infliximab, golimumab, adalimumab, vedolizumab, ustekinumab, ozanimod, upadacitinib, or tofacitinib for UC patients on high-dose 5-ASA maintenance therapy requiring two or more courses of corticosteroids in the preceding year or who developed corticosteroid dependence or refractory condition.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

Data from 16 RCTs comparing the TNFα antagonists, vedolizumab, tofacitinib, and ustekinumab to placebo as treatment options for UC were analyzed.[207] The results showed that all active interventions were superior to placebo for induction (RR: 1.62; 95% CI: 1.15–2.29) and maintenance of remission (RR: 2.28; 95% CI: 1.52–3.42). Furthermore, it was concluded that all medications were well tolerated with low rates of serious adverse events (RR: 0.44; 95% CI: 0.22–0.87).[207] It is to be taken into consideration that requiring steroids in patients on maintenance therapy is considered therapy failure.[177]

Ozanimod was also found to be superior to placebo, in a double-blinded RCT of 464 UC patients who failed 5-ASA and corticosteroids, at achieving clinical remission (23.4% vs. 8.9%), endoscopic improvement (35.6% vs. 14.9%), and MH (18% vs. 5%).[187] On its open long term extension, ozanimod showed response rates 34%–55% maintained over 2 years.[188]

Statement 68: We recommend using TNF inhibitors (certolizumab pegol, adalimumab, or infliximab), ustekinumab, or vedolizumab for adult patients with moderate-to-severely active CD to induce and sustain remission.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

Based on data from different clinical trials, TNF inhibitors, ustekinumab, and vedolizumab were

effective for induction and maintenance of remission in treatment-naïve adult patients with moderate-to-severely active CD.[150,214-216]

Statement 69: We recommend starting TNF inhibitors (infliximab, adalimumab, or certolizumab pegol), vedolizumab, or ustekinumab for patients with severely active CD who did not tolerate or had an inadequate response to conventional therapy, such as immunosuppressants or corticosteroids.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

Infliximab was reported to achieve sustained remission for up to 54 weeks in patients with severely active CD.[217] In the ACCENT I RCT, patients who responded to a single dose of 5 mg/kg IV infliximab were randomized to receive placebo at weeks 2 and 6 and then every 8 weeks till week 46, 5 mg/kg IV infliximab at weeks 2 and 6 and then 8 weeks till week 46, and 5 mg/kg IV infliximab at weeks 2 and 6 and then 10 mg/kg.[217] At week 30, remission was achieved in 21%, 39%, and 45% of the patients in the three groups, respectively.[217] The third group had the longest time to loss of response (54 weeks) in comparison to the first two groups (21 weeks and 38 weeks, respectively).[217]

Adalimumab efficacy in CD was assessed in CLASSIC I and II RCTs.[218,219] In CLASSIC I RCT, adalimumab was superior to placebo in achieving remission at week 4, where the remission rates were 18%, 24%, 36%, and 12% among the patients who received adalimumab 40 mg/20 mg, adalimumab 80 mg/40 mg, adalimumab 160 mg/80 mg, and placebo, respectively.[218] In CLASSIC II RCT, the long-term safety of adalimumab in active CD was assessed in 55 patients recruited from CLASSIC I trial.[219] At week 56, sustained remission was achieved in 79%, 83%, and 44% in the patients who received adalimumab 40 mg every other week, adalimumab 40 mg weekly, and placebo, respectively.[219]

Certolizumab pegol was reported to achieve a rapid remission and sustained response in patients with moderate-to-severe CD, regardless of the prior exposure to anti-TNF therapy and the use of concomitant medications.[220-223]

Vedolizumab efficacy in CD was studied in the GEMINI-2 RCT.[152] Remission at week 6 was achieved in 14.5% of the patients who received vedolizumab versus 6.8% of those who received placebo ($P = 0.02$).[152] At week 56, vedolizumab achieved sustained remission in 39% of those who received maintenance doses every 8 weeks and in 36.4% of those who received maintenance doses every 4 weeks, compared to only 21.6% sustained remission rate achieved among those who received placebo.[152]

The UNITI-1 and II trials evaluated the efficacy of ustekinumab in the treatment of patients with severe CD, who failed on conventional therapies.[224] Ustekinumab achieved sustained remission at week 44 in 53.1% of those who received maintenance doses every 8 weeks, in 48.8% of those who received maintenance doses every 12 weeks, and in 35.9% of those who received placebo.[224]

Statement 70: We recommend early initiation of biologic therapy in patients with CD with high-risk features.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

Early initiation of biologic therapy in CD, with high-risk features (detailed in Statement 36[129,130]), may help prevent disease-related complications.[225,226] In the *post hoc* analysis of the SONIC trial, early initiation of anti-TNF therapies was associated with significantly higher rates of achieving composite remission and MH in patients with extensive CD.[227] In the CHARM trial, initiation of adalimumab within the first 2 years was found to achieve clinical remission in 60% of the patients, whereas later initiation achieved remission in only 40% of the patients ($P < 0.05$).[228]

Statement 71: We recommend combining infliximab with methotrexate or thiopurine instead of using infliximab monotherapy for inducing and maintaining remission in active CD patients.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

Along with the previously discussed results of SONIC trial (in Statement 44),[149] another open-label RCT by

D'Haens *et al*.[229] randomized 133 patients to receive combined infliximab and azathioprine or conventional treatment (corticosteroids followed by azathioprine and infliximab). This trial showed that early combined therapy was superior to conventional therapy for the induction of clinical remission.[229] Corticosteroid-free remission was achieved in 60% of patients who received combined therapy and 35.39% in patients on conventional therapy ($P = 0.006$).

Statement 72: We recommend considering vedolizumab for patients ≥65 years old, patients with a history of a recent infection, and individuals at higher risk of infection or malignancy.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

Vedolizumab can be used as a monotherapy for the induction of symptomatic remission in patients with moderate-to-severely active CD.[214] It is considered particularly safe in elderly patients, patients with recent infections, and those with a high risk of infection or malignancy. In a study of 144 patients ≤40 years and 140 patients ≥60 years, the clinical response to vedolizumab was comparable between the two groups (40% vs. 35%, $P = 0.84$), but the older patients had significantly lower infection rates (2%) than the younger patients (12%) ($P = 0.002$).[230] The risk of infection and malignancy was reported to be significantly reduced in patients receiving vedolizumab.[220,231] The noted safety of vedolizumab is attributed to its selective action on $\alpha4\beta7$ integrins, that selectively block lymphocyte trafficking to the gastrointestinal tract.[221]

On the contrary, significant risks were reported to be associated with the use of anti-TNF therapies, corticosteroids, and thiopurines, for the treatment of IBD patients in many studies.[222] These risks include higher risks of malignancy and opportunistic infections in elderly patients.[223,232,233]

A meta-analysis by Bonovas *et al*.[234] evaluated the risk of infection and malignancy in adults with IBD, treated with various biologic agents. This meta-analysis showed that biologic agents were associated with an increased risk of opportunistic infections in patients with IBD, but not the risk of serious infections. Therefore, it is reasonable to accept the use of vedolizumab for individuals at higher risk of infection or malignancy who are under careful monitoring.[234]

Statement 73: If disease relapse occurs with vedolizumab therapy, dose escalation (by shortening dosing interval to every 4 weeks) should be considered while evaluating for co-existing or triggering factors.

Quality of evidence: Moderate; Grade: Moderate.

Strength of recommendation: Very strongly recommended (90% of panel strongly agreed).

In a retrospective study, Perry *et al*.[235] investigated the efficacy of vedolizumab dose escalation in a group of patients with UC. Among their cohort of 22 patients treated with vedolizumab, with a partial response to standard 8-weekly dosing, almost half (45%) were observed to achieve remission (partial Mayo score of 0 or 1) on dose escalation to 4-weekly. These findings are in accordance with a meta-analysis that demonstrated a random effects pooled efficacy rate of 53.8% for dose escalation if treated with vedolizumab.[150] This was also in accordance with the results from a small cohort study of 36 dose-escalated patients with CD or UC, which showed a response rate of 50%.[236]

Recent data, however, are contradictory to the current understanding. Preliminary results of the ENTERPRET phase IV clinical trial, presented at Digestive Disease Week 2022, showed that the endoscopic remission rate was not significantly different between a group of patients who received a maintenance dose vedolizumab at every 8 weeks (14.5%) and a group of patients who received an escalated dose at every 4 weeks (18.9%), after initial partial response on vedolizumab given at 6 weeks.[237]

Statement 74: If disease relapse occurs with ustekinumab therapy, dose escalation (typically by decreasing the dosing interval to every 4 weeks) should be considered while evaluating for co-existing or exacerbating factors.

Quality of evidence: Moderate; Grade: Moderate.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

Multiple recent studies have investigated the ustekinumab dose escalation for CD relapse. In a retrospective study by Kopylov *et al*.,[238] changing the dosing frequency of ustekinumab from 90 mg every 8 weeks to 90 mg

every 4 weeks in patients with CD improved clinical and biological indices of disease activity without severe adverse effects. On dose escalation, 28% achieved clinical remission and 36% had endoscopic remission.[238]

These results are in accordance with another retrospective study that evaluated the ustekinumab dose escalation strategy for selected CD patients who failed to achieve remission on a standard Q8 week regimen. The authors outlined that the dose escalation strategy improved clinical outcomes, prevented worsening disease severity, and positively affected CRP and albumin levels.[239] On dose escalation, the Physician Global Assessment (PGA) score improved with a mean of 0.47 ± 0.19, whereas the PGA scores of the patients maintained on Q8 week dosing regimen, worsened by a mean of 0.23 ± 0.23 ($P < 0.05$).[239] Additionally, a significant reduction of CRP (0.33 ± 0.19 mg/l) and a significant elevation of serum albumin (0.23 ± 0.06 g/dl) were noted on dose escalation ($P < 0.05$). Similarly, a multicenter retrospective cohort study assessed the effectiveness of dose escalation of ustekinumab and concluded that intensification of ustekinumab maintenance dosage was effective in more than 50% of the patients.[238]

The results from STARDUST trial,[240] however, were contrary to the previous results. In this randomized trial, Danese *et al*.[240] compared the outcome of 219 patients with CD randomized to receive a treat to target regimen, with the outcome of 221 patients randomized to receive the standard care. There was no significant benefit for escalating ustekinumab dose based on the treat-target approach with regard to endoscopic responses (38% vs. 30%, $P = 0.087$), endoscopic remission (11% vs. 15%, $P = 0.334$), MH (31% vs. 17%, $P = 0.449$), and clinical remission (62% vs. 70%, $P = 0.072$).[240]

Statement 75: We recommend optimizing the dose, switching to another anti-TNF agent, or switching to a different class, such as ustekinumab or vedolizumab, based on serum drug level (trough) and the presence of anti-drug antibodies (ADAs) in patients with secondary loss of response to anti-TNF therapy (and not primary treatment failure).

Quality of evidence: Moderate; Grade: Moderate.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

Most patients treated with anti-TNF therapy develop ADAs, which might result in loss of treatment efficacy. Approximately, 73% of infliximab-treated patients and 35% of adalimumab-treated patients develop ADAs.[241] Such a high percentage is attributed to the drug immunogenicity and the formation of anti-TNF antibodies, that reduce the treatment response over time.[242] This usually occurs within 12 months after the onset of treatment.[243] For infliximab, for example, the rate of loss of response was estimated to be 13% per year.[244] Therefore, the measurement of anti-TNF trough levels (TL) and the determination of ADA presence are frequently performed to optimize the management of patients with IBD.[245] Therapeutic drug monitoring (TDM) can be performed either during disease activity (reactive TDM) or in the setting of clinical remission to prevent future relapses (proactive TDM). To date, most of the literature studies support the use of reactive TDM rather than proactive drug monitoring. Large prospective trials, such as TAXIT and TAILORIX, failed to prove the benefit of proactive TDM[246,247]

The current guidelines recommend optimizing the dose or switching to another anti-TNF agent in patients failing anti-TNF therapy based on anti-TNF TL and presence of ADA.[19] Ustekinumab and vedolizumab are options for patients who have not achieved adequate response with anti-TNF agents, despite adequate drug concentrations, and can also be used as potential first-line treatments.[248]

In the GEMINI 1 trial of vedolizumab, more than 40% of patients with UC were prior TNF failures. In this study, the response rates at week 6 for vedolizumab versus placebo were 47% versus 25%.[150] However, the results from the post-hoc analysis showed response rates of 53% and 39% among patients naïve to anti-TNF treatment and those with prior exposure to anti-TNF drugs, respectively.[222] In the GEMINI 2 study, almost half of the recruited CD patients had previously failed anti-TNF therapy. After 6 weeks, the clinical remission rates were 14.5% and 6.8% among patients who received vedolizumab and those who received placebo, respectively. In the subgroup of patients who failed anti-TNF therapy, however, the remission rate was 15% compared to 12% of patients treated with placebo at week 6.[154]

The UNITI-1 trial evaluated patients with CD and included many patients with prior anti-TNF failure. The week 6 response was 34.3% and 33.7% for

patients treated with 130 mg or 6 mg/kg ustekinumab, respectively, versus 21.5% for the placebo group.[224] In UNITI-2, where most patients were naive to treatment, response to treatment was 52.7% and 55.0% for ustekinumab dosing of 130 mg or 6 mg/kg, respectively, versus 23.0% for placebo.[224]

Statement 76: We recommend switching to an alternative anti-TNF agent, in patients with low serum drug levels and positive ADAs, especially in the presence of high ADA titers.

Quality of evidence: High; Grade: High.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

In patients with low titers of ADAs, drug concentrations may remain high enough to be effective. However, in patients who develop high titers of ADAs, a substantial portion of the drug will be neutralized and is likely to produce a clinical non-response over time.[249]

Several studies support switching to a different anti-TNF agent for patients who developed high titers of ADAs as cross-immunogenicity does not occur among anti-TNF agents.[250,251]

A recent meta-analysis evaluated the efficacy and safety of a second anti-TNF agent (infliximab, adalimumab, or certolizumab-pegol) in patients with CD after primary/secondary failure or intolerance to a first drug. The indication for switching was the primary determinant for the efficacy of a second anti-TNF, i.e., the remission rates on using a second anti-TNF agent were significantly higher among patients who switched because of the intolerance (61%) compared to patients who switched because of the secondary (45%) or primary (30%) treatment failure.[252]

However, authors have suggested combination therapy rather than switching.[253] For instance, Roblin *et al*.,[253] in their RCT, compared the outcome in 90 patients who had an immune-mediated loss of response to anti-TNF therapies in two groups. The first group were randomized to receive combined azathioprine and anti-TNF therapy, whereas the second group was randomized to receive anti-TNF therapy only.[253] At 24 months, adding azathioprine to the anti-TNF therapy was associated with a higher survival rate without clinical failure (77% vs. 22%, $P < 0.001$) or development of unfavorable pharmacokinetics (78% vs. 22%, $P < 0.001$). These results might suggest that combination therapy should be offered initially for patients who develop immune-mediated loss of response. If this was intolerable or contraindicated, switching might be an alternative.

Statement 77: Patients with low serum drug levels and negative ADAs require dose optimization by either dose escalation or shortening the dosing interval.

Quality of evidence: Moderate; Grade: Moderate.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

Studies suggest that a low level of drug concentration can be overcome by dose escalation of anti-TNF therapy or the addition of an immunosuppressant. In a recent observational study, the authors evaluated different predictive external models to help individualize infliximab dosing regimens. The authors identified two models with the highest classification accuracy, which indicated dose escalation (for trough concentrations <5 μg/ml) in 88% of cases, thus, questioning population pharmacokinetic modeling to individualize infliximab dosing.[254]

Statement 78: We recommend for patients who do not respond to anti-TNF therapy although having adequate serum drug levels and negative ADAs (primary non-response [PNR]) to switch outside the anti-TNF class to another biologic agent.

Quality of evidence: Moderate; Grade: Moderate.

Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

For patients with PNR to one anti-TNF, the likelihood that they will respond to a second is low, and switching to a different class of drugs appears to be more appropriate. Results from a recent study reported that the drug levels in patients with PNRs were lower than the levels in responders. Accordingly, a considerable formation of antibodies within a few weeks of anti-TNF treatment initiation was suggested to be a significant factor that results in response failure in those patients.[255]

DISCUSSION

These adopted guidelines are the first to be released in the Kingdom of Saudi Arabia to help unify and improve diagnosis and management of IBD in the country. The guidelines were adopted mainly from the ECCO, ACG, AGA, and BSG

guidelines. They were developed by the Saudi Ministry of Health in collaboration with the SGA and the SCCP. The consensus recommendations included 78 clear statements about the diagnosis, classification, and treatment of IBD.

The consensus statements for the diagnosis of IBD recommended the use of a combination of clinical, biochemical, endoscopic (ileo-colonoscopy, sigmoidoscopy, EGD, VCE, or device-assisted enteroscopy), radiographic (MRI, CT, or IUS), and histological criteria for the diagnosis of IBD, but not genetic or serological tests. Differentiating other mimics of IBD was recommended via using stool analysis (to exclude enteric infection) and TB testing. The statements recommended using the Montreal and the Paris classification systems for adults and adolescents with IBD, respectively. Several tools were recommended for disease screening, assessment of disease activity, and evaluation of treatment response, such as clinical scores (HBI and PRO2), biomarkers (FC), endoscopic scoring systems (SES-CD and Mayo UC endoscopic subscore), radiological measures, and histologic scoring systems (RHI/NI).

Before starting advanced therapy, the consensus recommendations stated the importance of screening for latent TB. The guidelines covered aspects of co-treating latent TB in patients with IBD and included statements about when to use the "step-up" and when to use the "top-down" approaches for management of IBD based on the patient's risk profile.

For CD, the recommendations were to avoid using 5-ASA for induction and maintenance and to consider using oral budesonide (induction only), systemic corticosteroids (induction only), anti TNF therapies (infliximab, adalimumab, or certolizumab pegol) with or without a combined thiopurines, ustekinumab, or vedolizumab based on the patient's profile and response to conventional therapy. Thiopurines and methotrexate were recommended as maintenance therapy as corticosteroid-sparing agents in corticosteroid-dependent patients.

For UC, the guidelines recommended using 5-ASA derivatives (either oral or topical or both combined), budesonide MMX, corticosteroids, vedolizumab, infliximab, golimumab, adalimumab, ustekinumab, ozanimod, upadicitinib, tofacitinib, each detailed in specific patient profiles. The guidelines included statements about the contraindications of using the included disease-modifying drugs, and the selection criteria for each, and how to proceed in cases of failure on these therapies.

It is to be noted that these consensus recommendations were just confined to the evidence-based diagnosis and management of IBD. We did not include other, yet important, areas in practice, such as surgical management of IBD, management of emergency conditions, such as ASUC, guidance for delivering health care services for patients with IBD (including the structure of the health care unit, the role of different health care personnel, e.g., physicians, nutritionists, psychologists and psychiatrists, surgeons, pharmacists, and nurses), and guidance for the integration between primary, secondary, and tertiary health care. Some of these topics remain controversial and challenging. For instance, surgery is usually deferred for many patients, largely because of the lack of high-quality evidence for its role. Recent pivotal randomized clinical trials, such as the laparoscopic ileocolic resection versus infliximab treatment of distal ileitis in CD trial, would help restructuring physicians' thinking.[256] This would be considered in future updates of these consensus recommendations when more evidence about the role of surgery in IBD would have evolved. Future guidelines should, for example, include statements about the importance of having an IBD unit with a systemic operating protocol, that guarantees an access to an IBD-trained surgeon operating within the same center with shared/joint patient care for complex patients.

CONCLUSIONS

This review provides comprehensive, evidence-based consensus statements for gastroenterologists in Saudi Arabia, to diagnose and treat adult patients with IBD. The review comprises 78 clear statements covering the diagnosis of CD and UC, the classification of these diseases, and their treatment. Statements about treatment provided recommendations outlining the goals of treatment as well as the different treatment modalities provided, including 5-ASA derivatives, corticosteroids, immunosuppressants, biologics, and small molecules. The objective of these consensus statements is to unify and optimize the practice of IBD management in Saudi Arabia. Implementing these consensus statements in clinical practice would help the physicians appropriately diagnose, classify, uniformly manage, and improve IBD patient care.

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Conflicts of interest
Dr. Mahmoud Mosli received speaker fees, travel support and consultant honoraria from Janssen, AbbVie, Ferring, Takeda, Pfizer, Celgene, Novartis, Bristol-Myers Squibb,

Falk, and Hikma. Dr. Othman Alharbi received speaker and consultant honoraria from Janssen, AbbVie, Ferring, Pentax, Takeda, Pfizer, Celgene and Hikma, and travel support from Janssen, AbbVie, Ferring, Pentax, Takeda, Pfizer, Celgene. Dr. Shakir Bakkari received speaker and consultant honoraria from AbbVie, Johnson & Johnson, Takeda, Bristol-Myers Squibb, and Pentax. Dr. Turki AlAmeel received speaker honorarium from Janssen, AbbVie, Takeda, Pfizer, Amgen, Hikma; consultant honorarium from Janssen, AbbVie, Takeda, Pfizer, Bristol-Myers Squibb, Hikma and travel support from AbbVie, Takeda, Hikma. Dr. Badr Al-Bawardy received speaker honorarium from AbbVie, Takeda, Bristol-Myers Squibb; consultant honorarium from Bristol-Myers Squibb. All other authors declared no conflicts of interest regarding the publications of these recommendations.

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