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GUIDELINES AND CONSENSUS STATEMENTS

The Mexican consensus on the diagnosis and treatment of ulcerative colitis☆

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Abstract The guidelines presented herein are an updated version of the recommendations published in 2007. Since then, there has been a rapid advance in the knowledge about the pathophysiology of ulcerative colitis and its therapeutic options. New drugs have been approved, novel targeted therapies have emerged, and new strategies have been developed to improve the previously available approaches to the disease.

The aim of the present consensus is to promote the current knowledge of and Mexican perspective on the epidemiology, diagnosis, and medical and surgical treatment of chronic idiopathic ulcerative colitis.

The final vote on the statements and their ultimate modifications were carried out at the consensus working group meeting. Evidence was evaluated through the GRADE classification.
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◊ Members of the Mexican Consensus on Ulcerative Colitis Working Group can be found in the Appendix A.

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PALABRAS CLAVE
Colitis ulcerosa crónica idiopática;
Diagnóstico;
Tratamiento;
Epidemiología;
Colectomía;
Pouchitis

Consenso mexicano para el diagnóstico y tratamiento de la colitis ulcerosa crónica idiopática

Resumen Estas guías constituyen una actualización de las guías publicadas en 2007. Desde ese año, los conocimientos acerca de la fisiopatología, así como las opciones terapéuticas, han evolucionado rápidamente, con la aprobación de nuevos agentes, la aparición de nuevos blancos terapéuticos y nuevas estrategias para mejorar los abordajes disponibles previamente.

El objetivo de este consenso es promover una actualización y perspectiva mexicana sobre la epidemiología, el diagnóstico así como el tratamiento médico y quirúrgico de la colitis ulcerosa crónica idiopática.

Los enunciados fueron finalmente votados y se realizaron las modificaciones finales en la junta de consenso. La evaluación de la evidencia por la clasificación GRADE se realizó al momento del consenso.

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Introduction

Ulcerative colitis (UC) is a chronic disease of the colonic mucosa resulting from the interaction of genetic and environmental factors. Its clinical course is unpredictable and is characterized by episodes of remission and relapses or exacerbations. The exact epidemiologic data for the Mexican population are not known, but in recent years, disease incidence appears to be on the rise worldwide, especially in Western countries.[1]

The present guidelines are an update of those published in 2007.[2] Since then, there have been rapid advances in relation to the pathophysiology and therapeutic options of UC, with the approval of new agents, new therapeutic targets, and new strategies to improve the previously available approaches to the disease.

Aim

To promote a Mexican perspective on the epidemiology, diagnosis, and medical and surgical treatment of UC.

Methods

To develop the guidelines, Dr. Jesús Kazuo Yamamoto-Furusho designated a committee of 4 coordinators responsible for formulating 10 to 20 statements related to the epidemiology and etiopathogenesis, diagnosis, and medical and surgical treatment of UC, from the most recent information on the disease published in the medical literature.

A systematic search of the literature in English and Spanish was carried out for each of the statements formulated by the coordinators, using the Medline/Pubmed, Cochrane Database of Systematic Reviews, EMBASE (Ovid), and LILACS search engines. The search strategy included the following MeSH terms: epidemiology, risk factors, smoking, pathophysiology, diet, diagnosis, serum and fecal biomarkers, fecal calprotectin, endoscopy, radiology, biopsies, dysplasia, medical treatment, 5-aminosalicylates, immunomodulators, azathioprine, cyclosporine, steroids, prednisone, budesonide MMX, biologic treatment, infliximab, adalimumab, vedolizumab. All the randomized clinical trials, meta-analyses, systematic reviews, cohort studies, and case-control studies published within the last 20 years (1996-2016) were included.

The Mexican Consensus on Ulcerative Colitis Working Group was made up of 30 participants that included gastroenterologists, inflammatory bowel disease (IBD) specialists, colorectal surgeons, endoscopists, and pathologists. The coordinators of each area were in charge of developing the initial statements. An online platform (Survey Monkey) provided by Ferring Pharmaceuticals was utilized to interview the participants and modify the statements prior to the final face-to-face vote. A previous vote, employing the Delphi method, was carried out on the electronic platform to determine the level of agreement of the statements. Comments on specific references and suggested statement modifications were discussed. A final vote was conducted on the statements and the final modifications of the statements were made at the face-to-face consensus meeting. The quality (or certainty) of evidence and strength of recommendations were evaluated through the Grading of Recommendations Assessment, Development and Evaluation (GRADE) classification.

The face-to-face vote on the final statements and remaining data took place in Mexico City in one day. The statements were accepted when > 75% of the participants voted 4 or 5 on a scale of 1 to 5.

The recommendations were based on the level of evidence, according to the GRADE classification: Grade A, level of evidence 1, corresponding to randomized clinical trials; Grade B, level of evidence 2 or 3, corresponding to cohort studies or case-control studies; Grade C, level of evidence 4, corresponding to poor quality case series or cohort studies; and Grade D, level of evidence 5, corresponding to expert opinion.[3] The quality of evidence for each recommendation was classified as high, moderate, low, or very low. The grade of each recommendation was assigned as strong (utilizing the term ''recommend'')

or weak (utilizing the term ''suggest''). Recommendation strength was made up of 4 aspects: risk/benefit balance; patient preferences and values; resource availability; and quality of evidence.

Finally, the written document was approved by all the authors. The Consensus recommendations are written in bold and *italic* fonts, followed by comments on the evidence supporting the statement. Yamamoto-Furusho and Gutiérrez-Grobe were the physicians responsible for the final edition of the text.

1. Epidemiology and etiopathogenesis

Statement 1.1. Studies available in Mexico suggest a three-fold higher increase in the adjusted incidence rates of UC in the last twenty years. *Agreement percentage: 77%. LoE: IV. Grade of recommendation: C.*

Greater incidence and prevalence of inflammatory bowel diseases (IBDs) have been found in Northern Europe, the United Kingdom, and the United States.[4] However, an increase in cases of UC has been described in regions of low incidence, including Latin America.[5]

In a study by Yamamoto-Furusho published in 2009 that analyzed the epidemiology of UC in Mexico from 1987 to 2006, the mean of new cases increased from 28.8 within the first period (1987 to 1996), to 76.1 in the second period (1997 to 2006). Comparing the two periods, there was a 2.6-fold increase in incidence.[6] In addition, Bosques-Padilla et al.[7], in their study published in 2011, found that the rate adjusted to the number of hospital admissions to the Internal Medicine Service per year was 2.3, 2.6, 3.0, 3.6, and 4.1/1000 admissions, respectively, within the time frame of 2004 to 2008, at a hospital in Northwest Mexico.

Statement 1.2. The greatest incidence peak in Mexico is in patients between 20 and 40 years of age, equally affecting men and women. *Agreement percentage: 100%. LoE: IV. Grade of recommendation: C.*

In their study, Bosques-Padilla et al.[7] found that the most frequent patient age for disease presentation was between the third and fifth decades of life.

In his study, with respect to age distribution, Yamamoto-Furusho found one frequency peak between 21 and 30 years of age (37.1%) and another between 31 and 40 years of age (25.5%).[6]

Statement 1.3. Factors involving the environment, genetics, and the microbiota interact with the immune system in UC, resulting in altered responses that produce chronic bowel inflammation. Agreement percentage: 97%. LoE: IV. Grade of recommendation: C.

The key pathophysiologic mechanism of UC is a deregulated immune response to the commensal intestinal microbiome in a genetically susceptible host.[8] There is recent evidence that modern factors that modify lifestyle, such as antibiotic use, diet, smoking, and vitamin D metabolism, influence and modify systemic and intestinal immunity.[9] In addition, the genetic nature of IBDs has been widely recognized in different studies, and today more than 200 risk alleles have been identified in Caucasian populations. It is also known that some genetic polymorphisms act synergically with the environment and the microbiota and that the pathogenesis of IBD arises from the interaction between genetic, immunologic, and environmental factors.[10] In studies specifically conducted to identify the role of the microbiota in UC, dysbiosis has been observed to increase pathogenic and proinflammatory bacteria, and to generally be triggered by an event such as infectious gastroenteritis, in which there is an imbalance between commensal bacteria and pathogens, perpetuating an alteration in the epithelial intestinal barrier, causing translocation of bacteria and their products in genetically susceptible individuals.[11]

Statement 1.4. Genetic factors are related to UC pathogenesis, explained by the high frequency between first-degree relatives and the concordance rate found between monozygotic twins, compared with dizygotic twins. However, familial aggregation in Mexico is low, around 6.78%, compared with high-incidence populations. *Agreement percentage: 100%. LoE: III. Grade of recommendation: C.*

The authors of numerous studies have suggested that genetic factors play a role in the pathophysiology of UC. The sharing of susceptibility genes, as well as environmental factors, in members of the same family, appears to result in an increased risk of familial aggregation in relation to IBD.[12] High concordance rates for monozygotic twins, compared with dizygotic twins, have been reported in Northern European population cohorts, but there was a higher risk in patients with Crohn's disease, compared with UC. The concordance rates for UC in twins recently reported in European cohorts were approximately 15% for monozygotic twins and 8% for dizygotic twins.[13]

Familial aggregation has been widely documented in different population studies, ranging from 1 to 23%, depending on the case series and population. The familial aggregation rate has been reported to be higher in white patients, than in those of other ethnic groups.[14] In a Mexican study, Yamamoto-Furusho showed a low familial frequency of UC of 6.78%, compared with 13.4 to 15% that has been reported in Northern Europe and the United States.[6]

Statement 1.5. Altered intestinal permeability and dysbiosis in UC contribute to antigen exposure, resulting in the activation of multiple pathways that induce proinflammatory cytokine production. *Agreement percentage: 100%. LoE: II. Grade of recommendation: II-B.*

The gastrointestinal tract contains the largest microbial community of the body and numerous studies have

demonstrated that microbial genes influence gene expression in the host.[15] Increased immunity toward microbial antigens has been recognized in UC in different studies, and dysbiosis, or qualitative and quantitative abnormalities in the microbiota, has been observed.[16]

Statement 1.6. UC is characterized by the T_H2 and T_H17 helper cell response, with proinflammatory interleukin secretion. *Agreement percentage: 75%. LoE: II, Grade of recommendation: B.*

Helper T lymphocytes (T_H) possess plasticity and easily adapt to environmental stimuli, which is necessary for maintaining immunologic homeostasis. When that adaptability is lost or altered, restorative changes are impeded, and the immune response can trigger an uncontrolled chronic response.[9]

Under normal circumstances, dendritic and epithelial cell interaction promotes homeostasis through a noninflammatory T_H2 phenotype. However, UC is characterized by an atypical T_H2 response, with uncontrolled IL-5 and IL-13 production. And simultaneously, mucosal lymphocytes produce IL-17, stimulating T_H17 cell response. The T_H17 cells produce multiple cytokines, including IL-21 and IL-22. However, the T_H17 response is greater in Crohn's disease than in UC.[9]

Statement 1.7. International studies show that active smoking is not associated with the development of UC. Smoking does not have a significant impact on disease course. *Agreement percentage: 100%. LoE: II. Grade of recommendation: A.*

During the 1980s, it was established that tobacco smokers were less likely to develop UC than nonsmokers,[17] with up to a 3-fold greater risk for nonsmokers, according to a meta-analysis published in 1989.[18]

The effect of smoking on disease course had not been determined until the recent publication of a meta-analysis with a systematic review. Its results showed that smoking neither improved nor had a clinical impact on the natural history of UC. Due to that recent evidence and the beneficial health effects of smoking cessation, recommending that patients quit smoking, with no greater risk for the course of the disease, is suggested.[17]

Statement 1.8. Appendectomy has been demonstrated to protect against UC, perhaps through immunomodulating effects. Appendectomy in UC patients is not associated with reduced disease severity. The risk for colectomy in patients with UC and appendicitis is controversial. *Agreement percentage: 81%. LoE: III. Grade of recommendation: C.*

The authors of different studies have observed that early appendectomy is a protective factor against UC development, suggesting that the appendix plays a role in the pathogenesis of the disease. Nevertheless, there are studies in which appendectomy performed in patients older than 20 years of age was not protective, suggesting that the cells involved in UC development may extend beyond the appendix to another lymphoid tissue after that age.[19]

In earlier studies, UC was shown to behave less severely in patients after appendectomy.[20] However, in a recently published meta-analysis by Deng that analyzed 6 previous studies with a total of 4,994 patients, 434 of whom underwent appendectomy, the results of a subgroup analysis showed no significant difference in UC severity before or after appendectomy, regardless of disease extension (proctitis: OR 1.03, 95% CI: 0.74-1.42, p = 0.87; left colitis: OR 1.01, 95% CI: 0.73-1.39, p = 0.97; pancolitis: OR 0.92, 95% CI: 0.59, 1.43).[21]

The results of a recently published multicenter study demonstrated that appendectomy did not reduce UC severity, defined therein as the need for total colectomy, when compared with patients that did not have appendectomy. To the contrary, those authors reported that there was a 2.2-fold greater risk for colectomy in patients that underwent appendectomy after UC diagnosis.[21,22]

Statement 1.9. Nonsteroidal anti-inflammatory drugs, mainly naproxen, are associated with relapse in patients with UC. Aspirin, COX-2, acetaminophen, and nimesulide have not demonstrated that association. Oral contraceptives do not increase the risk for disease relapse or thrombosis. *Agreement percentage: 100%. LoE: III. Grade of recommendation: C.*

Cyclooxygenase-mediated epithelial barrier disruption in the intestine, caused by aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) has been described to affect the interaction between the microbiome and intestinal immune cells, affecting the risk for UC relapse. Despite the controversial nature of the studies, along with conflicting evidence, the majority have shown a slight increase in the UC relapse rate in NSAID users, and up to a 2-fold increased risk.[23]

In a recent cohort study, an association was found between NSAID use and relapse or exacerbation incidence, particularly in those patients using NSAIDS for more than 15 days per month, not counting aspirin, nimesulide, paracetamol, and some COX-2 inhibitors.[24] In line with that, clinical trials have been conducted to evaluate the safety and tolerability of the COX-2 inhibitors, especially celecoxib and etoricoxib, in patients with UC. The authors of those studies reported that the patients taking either etoricoxib or celecoxib, did not develop significantly more symptoms of UC exacerbation, compared with placebo.[25–27]

With respect to oral contraceptives (OCs) in IBDs, the results of a meta-analysis of studies carried out between 1980 and 2007 showed that current OC users had a minimal, but statistically significant risk for exacerbation of UC (RR:1.28, 95% CI: 1.26-1.70), adjusted for smoking and other factors.[28] Nevertheless, the authors of a systematic review of 5 more recent studies concluded that, despite the limited evidence, OC use did not increase the risk for relapse of IBDs. However, more studies on the subject are required, given that most of the evidence has come from patients with Crohn's disease.[29]

Statement 1.10. High intake of total fats (> 30 g/day), polyunsaturated fatty acids, and omega 6 fatty acids appears to confer a higher risk for UC. Optimum hygienic conditions apparently influence the increase of UC. *Agreement percentage: 94%. LoE: IV. Grade of recommendation: C.*

Because Western populations appear to be more affected by IBDs and the Western lifestyle has been associated with those diseases, the authors of different studies have suggested that high fat intake is a risk factor for developing UC.[30]

In their systematic review, Hou et al.[31] found a significant association between a high total fat intake and increased risk for UC. Likewise, they observed that monosaccharide and disaccharide consumption increased the risk for UC.

Environmental factors play an important role in the development of inflammatory diseases. First appearing in an article in 1989, the ''hygiene hypothesis'' initially was proposed with respect to the inverse correlation between hay fever and the number of older children in a household,[32] and it appears to be associated with different autoimmune diseases, as well as with inflammatory bowel diseases.[33]

In a recent meta-analysis by Cholapranee and Ananthakrishnan,[34] they found a protective association between Crohn's disease and different environmental hygiene measures, such as sharing a bedroom, sharing a bed, exposure to farm animals, having pets, and having numerous siblings. The authors suggested that the mechanisms of those protective factors included antigenic competition and the influence on regulatory T cell function, as well as modifications in the gut microbiome, causing greater diversity, and less susceptibility of the individual to IBDs.

2. Diagnosis

Statement 2.1. UC is diagnosed through the correlation of clinical, biochemical, endoscopic, and histopathologic aspects. *Agreement percentage: 100%. LoE: III. Grade of recommendation: C.*

The natural history of UC is characterized by episodes of relapse and symptom remission. UC diagnosis is made based on clinical suspicion, supported by macroscopic endoscopic findings and typical histologic findings in the biopsy. Infectious agents should be previously ruled out in stool exams.[35]

Statement 2.2. Chronic diarrhea with mucus and blood, straining and rectal tenesmus, nocturnal stools, weight loss, fever, and abdominal pain are the most frequent clinical symptoms. *Agreement percentage: 100%. LoE: III. Grade of recommendation: C.*

UC is a chronic inflammatory disease limited to the colonic mucosa, with a continuous extension pattern proximal from the rectum, and can extend throughout the entire colon. Diagnosis is based on clinical data, obtained from a detailed clinical history that should include information about the symptoms: symptom onset, presence of abdominal pain, pattern of diarrhea, extraintestinal symptoms, rectal bleeding, mucus and blood in stools, symptoms of straining and rectal tenesmus, weight loss, and general associated symptoms, such as fever. Important histories include: hygiene conditions, tobacco use, appendectomy, antibiotic use, and previous infections.

Clinical suspicion must be supported by biochemical data, such as elevated serum inflammation markers, signs of anemia, elevated fecal markers, and endoscopic and histologic data.[36]

Statement 2.3. Physical examination should include the measurement of vital signs, such as blood pressure, heart rate, body temperature, and weight, as well as abdominal examination to rule out peritoneal irritation. Anorectal examination and examination of the eyes, skin, and joints should also be carried out to search for extraintestinal manifestations. *Agreement percentage: 87%. LoE: IV. Grade of recommendation: C.*

The main characteristic of UC is the presence of mucus and blood in stools, accompanied by abdominal pain. Pain location depends on disease extension. Pain is generally present in the lower left quadrant in distal disease and extends to the entire colon as pancolitis. Abdominal distension and peritoneal irritation data upon palpation, accompanied by reduced intestinal noises, require continuous surveillance, given the high risk for presenting with toxic megacolon.[37]

Statement 2.4. A complete blood count, acute-phase reactants (erythrocyte sedimentation rate, C-reactive protein), liver function tests, and stool tests should be performed as the initial laboratory approach in patients suspected of presenting with UC. *Agreement percentage: 87%. LoE: III. Grade of recommendation: C.*

Complete blood count, inflammation markers including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), serum electrolytes, liver function tests, and stool samples for microbiologic analysis should be ordered for all patients in whom UC is suspected.[37]

The complete blood count reveals data of anemia, leukocytosis, and thrombocytosis. Acute-phase reactants are directly correlated with activity grade, in addition to helping predict outcomes and risk for colectomy.[38] Stool exams should be ordered to rule out frequent pathogens, such as *Clostridium difficile*, which can be complicating disease presentation.

Statement 2.5. A complete blood count to evaluate the grade of anemia and an assessment of iron kinetics to determine iron deficiency are suggested during follow-up. *Agreement percentage: 90%. LoE: III. Grade of recommendation: C.*

Anemia is the most frequent complication in patients with inflammatory bowel disease, with an average

prevalence of 18.6% (95% CI: 16.6-20.9). The majority of cases are mild-to-moderate, with mean hemoglobin of 11.3 ± 0.8 g/dl.[39] Anemia is one of the main factors associated with poor quality of life in patients with UC. It must be monitored, and its causes treated. The most frequent etiology of anemia in UC is iron deficiency, but it can also be caused by chronic disease anemia or a combination of the two.[40]

The risk for anemia is related to UC activity, and therefore measurements of ferritin, CRP, and complete blood count should be carried out every 6 to 12 months in patients with mild-to-moderate activity, and every 3 months in patients with active disease.[41]

Statement 2.6. Measurement of erythrocyte sedimentation rate, C-reactive protein, and fecal calprotectin levels is useful for evaluating UC activity and its medical treatment response. *Agreement percentage: 97%. LoE: III. Grade of recommendation: C.*

Acute-phase serum reactants and fecal calprotectin have been shown to be useful markers for evaluating disease activity and for predicting disease outcomes. In the severe exacerbation setting managed with intravenous steroid, a CRP > 45 mg/l at day 3, together with more than 8 stools per day, is predictive of colectomy.[42]

Furthermore, recent studies have shown that fecal calprotectin is correlated with endoscopic activity indices and is useful for evaluating treatment response, with 88% sensitivity (95% CI: 84-90%).[43]

Statement 2.7. Perinuclear anti-neutrophil cytoplasmic antibody determination (p-ANCA or its atypical pattern, x-ANCA) is suggested in UC patients, because it has been associated as a predictor of the development of pouchitis, disease extension, and extraintestinal manifestations, such as arthralgia. *Agreement percentage: 90%. LoE: III. Grade of recommendation: C.*

Even though the usefulness of diagnostic measurement of perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) for UC is low, there is a higher prevalence of p-ANCA antibodies in patients with UC than in patients with Crohn's disease. Those antibodies are incubated in neutrophils fixed with ethanol and analyzed through immunofluorescence. Their greatest usefulness is in making the differential diagnosis between UC and Crohn's disease, or in patients with nonspecific inflammatory symptoms. In addition, a higher prevalence of atypical ANCA (x-ANCA) than of p-ANCA has been observed in patients with UC (50 vs 32%), with high specificity (96%) and positive predictive value (99%).[44,45]

Some studies have shown that the presence of x-ANCA, as well as high levels of p-ANCA, are high-risk factors for developing pouchitis, as well as predicting disease extension and the presence of arthralgias.[44,46]

Statement 2.8. The genotyping of class II HLA alleles, such as HLA-DRB1*0103, HLA-DR15, and HLA-DRB1*0107, has been associated with clinical outcomes, including proctocolectomy, pancolitis, and steroid dependency in patients with UC. *Agreement percentage: 97%. LoE: III. Grade of recommendation: C.*

The genetic role in susceptibility for UC has been evaluated in numerous studies. Human leukocyte antigen (HLA) is one of the genes that plays a central role in immune response. The association between HLA polymorphisms and UC has been reported in studies conducted in Japan, the United States, and Europe.[47–50] In their study on Mexican patients, Yamamoto-Furusho et al.[51] observed increased frequency of HLA-DR1 polymorphisms in the group of patients with UC, compared with healthy controls (18.7 vs 5%; OR: 4.34; 95% CI: 1.95-9.86; p = 0.004). One of the associations found in that study was the increased frequency of HLA-DR15 in patients with pancolitis, compared with distal colitis (OR: 13.53; 95% CI: 1.4-267.4; p = 0.001). Likewise, patients that underwent proctocolectomy had a higher frequency of HLA-DRB1*0103, compared with patients that did not require surgical management (OR: 6.1; 95% CI: 1.32-22.67).

Statement 2.9. Fecal calprotectin and fecal lactoferrin levels are correlated with mucosal cicatrization or endoscopic remission and are predictors of UC relapse. *Agreement percentage: 97%. LoE: II. Grade of recommendation: B.*

Fecal markers indicate the presence of intestinal inflammation, but they are not specific for IBD. Their greatest usefulness is in monitoring carried out after diagnosis. Calprotectin is a protein derived from neutrophils and its excretion in feces at very high cutoff values, especially above 200 mcg/g, has 84% sensitivity and 96% specificity for IBD, with a 95% positive predictive value.[43,52]

In that context, the authors of a recent meta-analysis reported that there was 78% sensitivity and 73% specificity for predicting relapse in patients with quiescent IBD.[53]

Statement 2.10. Ova and parasite exam with 3 separate stool samples, stool culture, and *Clostridium difficile* toxin A/B test are suggested in cases of active UC or relapse to rule out an infectious process as the cause of disease exacerbation. *Agreement percentage: 87%. LoE: III. Grade of recommendation: C.*

Stool exams should be performed in patients with relapse, because it is known that *C. difficile* and cytomegalovirus infections are associated with higher mortality and a lack of treatment response.[54]

In a study conducted on a Mexican population, a 61.4% frequency of positive stool exams was found in patients with active UC. Infection associated with disease reactivation was correlated with negative outcomes in relation to treatment response and hospitalizations.[55]

Statement 2.11. Plain abdominal x-ray to rule out toxic megacolon and a chest x-ray to rule out colon perforation

should be considered in patients with severe UC. *Agreement percentage: 97%. LoE: III. Grade of recommendation: C.*

Plain abdominal x-ray and chest x-ray should be considered in the evaluation of patients with acute abdominal pain and computed axial tomography should be contemplated in patients in whom toxic megacolon or perforation is suspected, as well as in patients with inconclusive biochemical tests. Signs of colonic dilation greater than 6 cm in the transverse colon should be looked for when megacolon is suspected.[56]

Statement 2.12. The most widely used clinical indices for evaluating the grade of UC activity are the Truelove and Witts index and the Mayo score. *Agreement percentage: 88%. LoE: III. Grade of recommendation: C.*

There are different instruments for the clinical evaluation of UC activity.[57] The original classification system for severe UC was proposed by Truelove and Witts in 1955.[58] It continues to be the gold standard for rapidly identifying patients that require immediate hospital admission, as well as an instrument for therapy modification.[45]

Another widely used scale is the Mayo score, based on a scale from 0 to 12 points. It considers clinical characteristics, the overall evaluation of the physician, and endoscopic aspects. There is a shorter version of the scale that does not include endoscopic data.[59]

Because those scales provide a cross-sectional evaluation of the UC patients, meaning at a single point in time, the future trend will be to validate scales that take into account the course of the disease and the grade of incapacity and altered quality of life, among other important aspects, in the patient with UC.[57]

Statement 2.13. Colonoscopy with ileocecal valve intubation is the diagnostic method of choice for evaluating the extension and grade of disease activity. In cases of severe UC activity, only flexible rectosigmoidoscopy is recommended for taking biopsies. *Agreement percentage: 87%. LoE: III. Grade of recommendation: C.*

Ileocolonoscopy with biopsy is the most important diagnostic test when UC is suspected. Changes proximal from the anal verge are observed and involvement is characteristically continuous and confluent.

Statement 2.14. The most characteristic endoscopic findings in the acute phase are loss of the vascular pattern, erythema, friability, erosions, and ulcerations of the mucosa. In the chronic phase, they are pseudopolyps and a tubular shape of the colon. Mucosal compromise is continuous in the majority of the cases. *Agreement percentage: 97%. LoE: III. Grade of recommendation: C.*

Even though there are no pathognomonic lesions at endoscopy, lesion aspect tends to be a continuous pattern of ulcerated and friable mucosa, with erosions and vascular pattern loss. A tubular shape of the colon and pseudopolyps of the mucosa are characteristic of chronic stages.[60]The most recent reports in the literature suggest the performance of colonoscopy and rectosigmoidoscopy for taking biopsies in the context of the patient with relapse and the patient that is treatment-refractory. Biopsy is also suggested for follow-up and ruling out cytomegalovirus.

Statement 2.15. At least two biopsies should be taken per segment at the level of the terminal ileum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum, including normal zones of the mucosa, to microscopically make the diagnosis and determine disease extension. *Agreement percentage: 93%. LoE: III. Grade of recommendation: C.*

Multiple biopsies of at least 6 segments of the colon are required for histologic diagnosis: the terminal ileum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum. The biopsies should be taken at endoscopically obvious active and inactive sites.[61] They should be fixed in formaldehyde and separated by segment in different vials, accompanied by the clinical data of the patient and the endoscopic findings.

Statement 2.16. Histopathologic findings suggestive of UC are: crypt architectural distortion, lamina propria lymphoplasmacytic infiltrate, cryptitis, crypt abscesses, and goblet cell depletion. *Agreement percentage: 100%. LoE: III. Grade of recommendation: C.*

Microscopic diagnosis of UC is based on the distortion of crypt architecture, diffuse inflammatory infiltrate with basal plasmacytosis, cryptitis data with crypt branching and crypt abscesses, as well as mucin depletion due to a reduction of goblet cells. Up to 20% of patients with fulminant UC can have ulcers that penetrate into the muscularis propria. The finding of basal plasmacytosis usually helps differentiate UC from infectious colitis due to the frequency of those cells: 63% vs 6%, respectively.[61,62]

Statement 2.17. Dysplasia should be evaluated through the Vienna classification by at least two pathologists. *Agreement percentage: 97%. LoE: III. Grade of recommendation: C.*

Dysplasia is defined as neoplastic epithelium with no signs of tissue invasion and is the most relevant marker for risk of malignancy in patients with UC. Dysplasia associated with UC develops in zones of chronic inflammation. For diagnostic purposes, the use of the 2000 Vienna classification is suggested, to facilitate staging into the following categories: 1: non-dysplastic mucosa; 2: undefined dysplastic lesions; 3: low-grade noninvasive neoplasia; 4: high-grade noninvasive neoplasia.[61]

Due to great interobserver variability in biopsy evaluation, it is suggested that at least two expert gastrointestinal pathologists evaluate the biopsies.[63]

Statement 2.18. Dysplasia or colorectal cancer surveillance in patients with UC should be carried out through

colonoscopy at 8 years from symptom onset in cases of pancolitis, at 12 years from symptom onset in cases of left colitis, and annually from the diagnosis of primary sclerosing cholangitis. *Agreement percentage: 93%. LoE: Va. Grade of recommendation: D.*

The risk of colorectal cancer (CRC) in patients with UC is increasing, in comparison with the general population. The risk is associated with duration and the grade of disease activity. The accumulated risk for CRC has been reported to increase from 7 to 18% at 30 years.[64,65] According to the recent literature, surveillance colonoscopy has an impact on the risk for CRC.[66] Yearly surveillance colonoscopy should be performed on patients with primary sclerosing cholangitis from the time of diagnosis.

Statement 2.19. Magnification chromoendoscopy with indigo carmine or methylene blue is recommended for the detection of flat lesions associated with dysplasia. If the necessary equipment or experienced personnel is not available, biopsies should be taken in the four quadrants every 10 cm up to the descending colon and every 5 cm in the sigmoid colon and rectum. *Agreement percentage: 97%. LoE: II. Grade of recommendation: B.*

The current recommendation is to take random biopsies, as well as targeted biopsies in visible lesions, during white-light colonoscopy, but targeted biopsies are suggested when using chromoendoscopy, because that method appears to increase the detection rate of dysplasia.[67] Chromoendoscopy with indigo carmine dye improves the dysplasia detection rate, producing enhancement of subtle vascular and mucosal changes.[68] The diagnostic yield of indigo carmine dye is similar to that of methylene blue. Nevertheless, in centers that lack experience with chromoendoscopy, or that do not have the equipment for the technique, the suggestion is to continue screening with random biopsies. A recent study suggested that random biopsies are equally as efficacious as targeted ones in detecting neoplasia in endoscopic surveillance.[69]

Statement 2.20. Endoscopic resection of the mucosa is recommended for lesions that are detected during follow-up colonoscopy and classified using the Paris classification, in patients with UC. *Agreement percentage: 97%. LoE: III. Grade of recommendation: C.*

Lesion resectability is the most important characteristic in making therapeutic and surveillance decisions in UC. At present, the Paris classification provides a more simplified way of classifying UC lesions. In lesions detected during colonoscopy, current guidelines suggest treatment with endoscopic dissection of the submucosa or endoscopic resection of the mucosa.[70] The suggested surveillance interval after endoscopic treatment is < 1 year in patients with flat or sessile lesions and serrated polyps > 15 mm. Surveillance at 3 to 6 months is recommended in patients with larger lesions. Annual surveillance colonoscopy is suggested for patients with small polypoid lesions.[67]

3. Medical treatment

Statement 3.1. The 5-aminosalicylates (5-ASA) are the first option for inducing remission in mild-to-moderate relapse and for maintaining remission in patients with UC. *Agreement percentage: 100%. LoE: I. Grade of recommendation: A.*

Oral 5-ASA efficacy for inducing remission in patients with active mild-to-moderate UC is supported in two meta-analyses. The first included 8 studies and demonstrated a relative risk (RR) for no remission of 0.86 (95% CI: 0.81-0.91) and the second meta-analysis, with 11 studies, had a RR of 0.79 (95% CI: 0.73-0.85). A dose > 2.0 g/day was more efficacious than a dose < 2.0 g/day (RR: 0.91; 95% CI: 0.85-0.98).[71,72]

Statement 3.2. 5-ASA suppositories at a dose of 1 g per day are recommended as first-line treatment in patients with mild-to-moderate proctitis (UC) to induce symptom remission. *Agreement percentage: 93%. LoE: I. Grade of recommendation: A.*

A meta-analysis of 38 studies on patients with active mild-to-moderate UC included 10 studies in which rectal 5-ASA was applied versus placebo.[73–78] Rectal 5-ASA was superior to placebo for achieving symptom remission with a RR of 8.3 (95% CI: 4.28-16.12; $p < 0.00001$) and endoscopic remission with a RR of 5.3 (95% CI: 3.15-8.92; $p < 0.00001$).[71]

The use of rectal 5-ASA was superior to the rectal administration of steroids for inducing symptom remission with an odds ratio (OR) of 1.6 (95% CI: 1.1-2.45; $p < 0.01$).[79]

Statement 3.3. Oral 5-ASA at a dose of 2 to 4.5 g per day is recommended as first-line treatment in patients with active mild-to-moderate UC at any extension beyond that of proctitis for inducing complete remission. *Agreement percentage: 96%. LoE: I. Grade of recommendation: A.*

Results from the ASCEND study (n=1459) showed no significant difference in clinical improvement with doses of 2.4 g or 4.8 g per day of mesalazine in the overall analysis, but in the subgroup analysis, the patients with moderate disease activity benefitted from the higher dose.[80–82]

Statement 3.4. The combination of oral 5-ASA at a dose of 2 to 4.5 g/day and topical treatment with mesalazine at a dose of 1 to 4 g/day is recommended over oral treatment alone in patients with active mild-to-moderate UC at any extension beyond that of proctitis to induce remission. *Agreement percentage: 84%. LoE: I. Grade of recommendation: A.*

The authors of a meta-analysis of 4 randomized controlled trials on patients with active mild-to-moderate UC reported that the combination of oral and rectal 5-ASA was superior to monotherapy with oral 5-ASA for inducing remission, with a RR for no remission of 0.65 (95% CI: 0.47-0.91). There was no significant difference in the adverse event rate

between the patients that received the combination therapy (22.3%) and those that received monotherapy with oral 5-ASA (26.9%) (RR: 0.77; 95% CI: 0.55-1.09).[74]

Statement 3.5. Symptom response to treatment with 5-ASA in patients with mild-to-moderate UC is recommended to be evaluated at 4-8 weeks to determine the need for treatment modification. *Agreement percentage: 100%. LoE: I. Grade of recommendation: A.*

The randomized controlled trials of treatment with 5-ASA in patients with active UC have shown that approximately 10 to 30% of patients presented with symptom remission at treatment week 2; 30 to 45% at week 4; and 45 to 50% at week 8.[83,84]

Almost 75% of the patients with proctitis or left colitis will present with at least one relapse within the period of one year, underlining the importance of maintenance therapy. Meta-analyses have demonstrated the efficacy of maintenance therapy with 5-ASA in those patients.[85,86] In an analysis of 7 randomized controlled trials on patients treated with 5-ASA an average of 6 to 24 months, maintenance therapy with rectal 5-ASA was associated with a RR for relapse of 0.60 (95% CI: 0.49-0.73; number needed to treat [NNT] of 3), compared with placebo.[85] A dose of 5-ASA $>$ 2.0 g/day appears to be more effective than a dose $<$ 2.0 g/day to prevent a relapse (RR: 0.79; 95% CI: 0.64-0.97).[87]

Important clinical differences in efficacy and safety between the different 5-ASA formulations for UC induction and maintenance treatment have not been described in meta-analyses. No benefit has been reported in switching to another 5-ASA formulation in patients that have not achieved remission with 5-ASA treatment.[87,88]

No significant difference was found in a 3-study meta-analysis in relation to the efficacy rate or adherence rate of induction treatment with dose administration once a day, or its fragmentation, with a RR for no remission of 0.95 (95% CI: 0.82-1.1).[89]

There was no significant difference in relapse rates for single-dose 5-ASA or a regimen 2 to 3 times a day in a meta-analysis of 7 randomized controlled trials, with a RR of 0.94 (95% CI: 0.82-1.08).[90]

Statement 3.6. Oral budesonide MMX at a dose of 9 mg/day is suggested as alternative treatment in patients with mild-to-moderate UC at any extension beyond that of proctitis to induce clinical remission. *Agreement percentage: 84%. LoE: II. Grade of recommendation: B.*

Moderate-quality studies support the administration of budesonide MMX to induce remission with or without concurrent 5-ASA treatment. In addition, the formulation appears to be safe and does not cause adrenocortical dysfunction. Nevertheless, another moderate-quality study indicated that 5-ASA was superior. Because the collected evidence is limited, new studies are needed to confirm its efficacy for inducing remission in patients with mild-to-moderate UC activity, despite high doses of 5-ASA.[91]

Statement 3.7. Oral systemic steroids are recommended as second-line treatment to induce clinical remission in patients with any extension of mild-to-moderate UC that have had 5-ASA treatment failure. *Agreement percentage: 83%. LoE: I. Grade of recommendation: A.*

Evidence of the benefit of oral steroid therapy (prednisone 40 mg/day) was that it induced remission in 76% of 118 patients with mild-to-moderate UC, compared with 52% of patients treated with sulfasalazine 8 g/day.[92]

Statement 3.8. Oral corticoids are not recommended for patients with UC to maintain remission because they are not effective, and their prolonged use is associated with important adverse effects. *Agreement percentage: 96%. LoE: I. Grade of recommendation: A.*

A suggested regimen for moderate disease is prednisone 40 mg/day or 0.5 to 1 mg/kg/day for 4 weeks, with a gradual 5-mg reduction per week. The shortest therapies (fewer than 3 weeks) are associated with a high early relapse rate. The continuous administration of systemic steroids at doses above 20 mg/day is not recommended for more than 6 months, due to increased adverse reactions.

Statement 3.9. Oral steroids are recommended as first-line treatment for inducing remission in patients with active moderate-to-severe UC. *Agreement percentage: 93%. LoE: I. Grade of recommendation: A.*

The efficacy of that maneuver has been documented in two controlled studies with placebo vs conventional steroids in ambulatory patients with active UC, with a number needed to treat (NNT) of 2 (95% CI:1.4-5).[93,94] The clinical benefit of standard steroids over placebo for achieving clinical remission of UC was confirmed in a meta-analysis.[72]

Statement 3.10. The evaluation of symptom response to induction therapy with corticoids is recommended after 2 weeks to determine the need for treatment modification in patients with UC. *Agreement percentage: 100%. LoE: I. Grade of recommendation: A.*

The working group of the consensus believes there should be a standard guide to determine how to recognize both steroid dependence and steroid refractoriness.

Statement 3.11. Thiopurines are suggested for corticoid-free complete remission maintenance in patients with UC that have achieved symptom remission with oral corticoids. *Agreement percentage: 97%. LoE: II. Grade of recommendation: B.*

In steroid-dependent UC patients, both thiopurines and azathioprine are significantly more effective for achieving clinical and endoscopic remission than mesalazine. In a study in which 72 patients randomly received azathioprine 2 mg/kg/day or oral mesalazine 3.2 g/day plus prednisolone 40 mg/day,[95] 53% of the azathioprine group achieved steroid-free remission and endoscopic remission after 6 months,

compared with 21% of the mesalazine group, with an OR of 4.78 (95% CI: 1.57-14.5). In addition, in an open, observational cohort study with 42 steroid-dependent patients, there was steroid-free remission at 12, 24, and 36 months in 55, 52, and 45% patients, respectively.[96] Thus, thiopurines should be first-line therapy in patients that have recurrence after steroid suspension.

Statement 3.12. Anti-TNF is recommended for inducing complete steroid-free remission in UC patients that do not respond to corticoids or thiopurines. *Agreement percentage: 100%. LoE: II. Grade of recommendation: B.*

In the ACT 1 and 2 studies, 56% of the patients were under treatment with steroids upon enrolling in the study,[97] even though the dose could have been sub-optimal. At week 30, a significant number of patients that received infliximab vs placebo achieved steroid-free remission (21 vs 7%; p = 0.01). At one year (only in ACT 1), the rates were 26 and 9%, respectively (p = 0.006).

Statement 3.13. Anti-TNF therapy for inducing and maintaining complete steroid-free remission is recommended in steroid-dependent patients with UC. *Agreement percentage: 96%. LoE: II. Grade of recommendation: B.*

In patients with steroid-dependent or steroid-refractory active UC, other persistent symptom causes should be considered, such as the coexistence of cytomegalovirus infection, *C. difficile* infection, or cancer. If steroid-dependent or steroid-refractory UC is confirmed, an alternative therapy is required to induce steroid-free remission. There is clear evidence that anti-TNF therapy is useful in that group of patients. The ACT 1 and ACT 2 studies included 334/728 (46%) patients with immunomodulator-refractory disease.[97] Infliximab at either dose (5 or 10 mg/kg) provided clinical remission in a significantly higher number of patients at week 8 vs placebo, even though the exact number of subgroup immunomodulator-refractory patients was not reported.

Statement 3.14. When anti-TNF therapy is begun, monotherapy or combination therapy with thiopurine, depending on the anti-TNF agent used, is recommended to induce clinical and endoscopic remission. *Agreement percentage: 96%. LoE: II. Grade of recommendation: B.*

In the UC-SUCCESS study on patients under treatment with immunomodulators, it was more likely for the patients receiving the combination of azathioprine and infliximab (induction and maintenance therapy) to be in steroid-free remission after 16 weeks, than the patients receiving monotherapy with infliximab.[98]

According to a Cochrane group systematic review of 7 trials on the efficacy of infliximab for treating steroid or immunomodulator-refractory moderate-to-severe UC, the conclusion was that infliximab (intravenous infusion at weeks 0, 2, and 6) was more effective than placebo for inducing clinical remission at week 8, with a RR of 3.22, (95% CI: 2.18-4.76).[99] However, the benefit in the subgroup of immunomodulation therapy-refractory patients was not reported.

At present, there are no studies investigating whether or not the combination treatment of adalimumab or golimumab with thiopurines is superior to monotherapy in patients with UC.

Statement 3.15. Evaluation of lack of symptom response to induction anti-TNF therapy in UC patients is recommended at 8 to 12 weeks to assess the need for treatment modification. *Agreement percentage: 100%. LoE: II. Grade of recommendation: B.*

The majority of clinical trials evaluate a response to biologic agents at the second week of treatment, and significant improvement has been found with those agents between weeks 2 and 4, compared with placebo.[98] Higher remission rates at week 8 have been reported in randomized trials that include induction therapy, and they have been reported at week 16 in trials with adalimumab. Therefore, when utilizing biologic agents, the suggestion is to evaluate the lack of treatment response at weeks 8 to 12.[100,101]

We suggest symptom evaluation and the inclusion of colonoscopy, albeit no ideal time for its performance has been established. Likewise, earlier re-evaluation of patients with severe UC should be considered.

Statement 3.16. The recommendation for patients that respond to anti-TNF induction therapy is to continue with that therapy to maintain complete remission. *Agreement percentage: 97%. LoE: II. Grade of recommendation: B.*

Biologic agents were efficacious for maintaining remission in UC at one year of treatment in 35% of patients vs 16% of patients treated with placebo.[98] Maintenance of clinical remission in up to 90% of patients has also been reported in open studies.[102] Remission maintenance with other biologic agents, such as adalimumab, has been demonstrated in 31% of UC patients at one-year follow-up.[103,104]

A total of 23-28% of patients treated with golimumab (PURSUIT) maintained remission at one year, compared with 15.6% in the placebo group (p = 0.004).[105]

There was an important risk for opportunistic infections with the use of biologic agents of 3% vs 0.9% in patients that received placebo, with a RR of 2.05; (95% CI: 1.10-3.85), and that risk tended to be even higher with the combination of biologic agents plus steroids or immunomodulators. With adequate prevention measures and correct screening before the administration of those medications, followed by periodic surveillance, the risk for infections, neoplasias, and other adverse effects related to their use can be minimized in patients with UC.[106]

Long-term or indefinite use of biologic medications in the patient with UC is a controversial theme. Its efficacy in most reports is described up to one year, but there is no opinion or consensus on the subject. Therefore, the working group of the Mexican consensus suggests that their indefinite use be maintained, within the individualized context of the patient, until the medication ceases to be effective.

In a recent multinational, retrospective cohort study, the suspension of infliximab in patients with UC was associated with a higher relapse rate (23.3 vs 7.2 per 100 patients/year vs 7.2 of the control group) with a hazard ratio of 3.70 (95% CI: 2.02-6.77). However, upon reinitiating the medication, 77.1% had treatment response and 51.4% achieved remission.[107]

Statement 3.17. Dose optimization through measuring therapeutic drug levels and immunogenicity is recommended in patients with sub-optimal response to anti-TNF therapy. *Agreement percentage: 100%. LoE: II. Grade of recommendation: B.*

It is vital to know that there is a proportional relation between mucosal healing, induction probability, and remission maintenance and the serum biologic agent levels. In relation to patients with an initially inadequate response, it is important to be aware that the lack of response during induction can be improved through intensifying the dose regimen, which can be achieved by shortening the interval between doses or increasing the weight-adjusted dose, before considering it a primary anti-TNF failure.[108]

During regimen maintenance, a secondary loss can be the result of low medication levels (45%) or the formation of antibodies against the biologic agent (17%).[109,110]

In patients with low medication levels, scaling the dose was associated with response in up to 86% of patients, whereas 17% of patients with biologic agent antibodies responded. Likewise, dose optimization resulted in a symptom response in 67% of patients treated with adalimumab that had low medication levels. Therefore, dose optimization should be considered in patients with treatment failure, and when possible, decisions should be based on serum levels of the medication and the presence of antibodies against it.[111]

Statement 3.18. The use of vedolizumab to induce complete steroid-free response, rather than another anti-TNF drug, is recommended in patients with primary anti-TNF therapy failure. *Agreement percentage: 93%. LoE: II. Grade of recommendation: B.*

In relation to the treatment of patients with conventional biologic treatment failure, despite dose intensification, there are still no studies that directly compare switching to vedolizumab, an anti-integrin molecule, or to an alternative anti-TNF formula. The available observational evidence suggests that switching to a different anti-TNF agent may be more effective in patients that develop anti-TNF antibodies and less effective in patients with primary failure.[110,112,113]

Statement 3.19. To induce complete steroid-free remission in patients with secondary anti-TNF therapy failure, changing the anti-TNF therapy or switching to vedolizumab, based on the results of therapeutic drug level monitoring and immunogenicity, is recommended. *Agreement percentage: 100%. LoE: II. Grade of recommendation: B.*

Because the mechanism of action of vedolizumab is different from that of anti-TNF drugs, it is possible for that kind of agent to be more effective in patients with primary or secondary anti-TNF failure.

Statement 3.20. Vedolizumab is recommended to induce complete steroid-free remission in patients with active moderate-to-severe UC that present with steroid, thiopurine, or anti-TNF treatment failure. *Agreement percentage: 100%. LoE: II. Grade of recommendation: B.*

During the induction phase of the GEMINI I study, 374 patients previously treated with corticosteroids, immunomodulators, or anti-TNF therapy were randomly assigned to receive vedolizumab or placebo.[114] At week 6, the vedolizumab group showed superior remission rates, compared with the placebo group (16.9% vs 5.4%; p< 0.001) and higher figures in the failed anti-TNF therapy group (9.8% vs 3.2%), the steroid group (21.4% vs 0%), and the immunomodulatory group (21.9% vs 10.9%).[114,115] The symptom response rate for vedolizumab was also superior in the total population (47.1% vs 25.5%; p < 0.001), and in the groups that had treatment failure with anti-TNF drugs (39.0% vs 20.6%) or corticosteroids (59.5% vs 20.0%).[115] The consensus working group concluded that vedolizumab is a useful option in patients that have had prior treatment failure with corticosteroids, immunosuppressants, or anti-TNF agents. There are no available data on which strategy to use in patients with vedolizumab treatment failure, but an anti-TNF regimen could be considered. Colectomy continues to be an option to contemplate in patients that do not respond to medical therapies or that have prolonged corticosteroid dependence.

Statement 3.21. The evaluation of lack of symptom response to induction therapy with vedolizumab in UC patients is recommended at 8 to 14 weeks to determine the need for treatment modification. *Agreement percentage: 97%. LoE: II. Grade of recommendation: B.*

In the GEMINI I study, vedolizumab showed a statistically significant symptom response rate, compared with placebo at week 6 (47.1% vs 25.5%; 95% CI: 11.6-31.7; p < 0.001).[114] Improvement in the partial Mayo score reached its maximum level at week 6 and remained unchanged throughout the maintenance phase and with minimal change thereafter. The consensus working group considers that in clinical practice, follow-up evaluation should be before the first dose in the maintenance phase and recommends that symptom response be evaluated at weeks 8 to 14. That recommendation does not exclude early individual patient evaluation, especially with respect to tolerance, if clinically indicated.

Statement 3.22. Apart from a clinical trial, fecal microbiota transplantation is not recommended in patients with UC to induce or maintain complete remission. *Agreement percentage: 97%. LoE: III. Grade of recommendation: C.*

There is not enough evidence to support the use of fecal microbiota transplantation (FMT) in patients with UC.

Nevertheless, there are case reports that suggest its benefit.[116] The preliminary analysis of the first controlled clinical trial of FMT on 63 patients with active UC did not show benefits at week 7.[117] Some patients reported subjective improvement and after continuing treatment to week 12, 33% of the patients achieved complete remission. A position statement of the Canadian Association of Gastroenterology recommended that in the absence of controlled data clearly demonstrating efficacy, FMT as treatment for UC should only be used in the clinical trial setting.[116] Until its usefulness is based on solid scientific evidence, the present consensus working group is against the use of FMT in clinical practice.

Statement 3.23. Apart from the clinical trial setting, we do not recommend probiotics for remission induction or maintenance in patients with UC. *Agreement percentage: 100%. LoE: III. Grade of recommendation: C.*

In a meta-analysis that included 23 controlled clinical trials, probiotics, primarily used as adjuvants in 5-ASA management or immunomodulating therapy, significantly increased the remission rate in UC patients, with a RR of 1.80 ($p < 0.0001$).[118] That beneficial effect was apparent only with VSL#3.[118,119] In another meta-analysis of 3 experimental studies, VSL#3 added to conventional therapy resulted in a higher remission rate than conventional therapy alone (43.8% vs 24.8%; OR: 2.4; 95% CI: 1.48-3.88; $p = 0.0001$).[119] A recommendation supporting the use of probiotics could not be made, given the poor quality of the individual studies included in the meta-analyses.

Statement 3.24. Patients with severe UC should be hospitalized and evaluated by experienced physicians for their optimum treatment. *Agreement percentage: 93%. LoE: Vb. Grade of recommendation: D.*

Severe UC is a potentially life-threatening condition. The historic data on that clinical setting in UC show that 47/250 (18.8%) initial relapses are severe. In addition, at least 17.6% of patients are estimated to have had a severe acute episode at some point during the course of the disease.[120] The present consensus working group believes that all patients that meet the severe UC criteria should be admitted to a hospital to receive intensive medical treatment under the care of a multidisciplinary team that includes a gastroenterology specialist and a colorectal surgeon.

Statement 3.25. Intravenous steroids should be first-line treatment for patients with severe UC. Agreement percentage: 100%. LoE: I. Grade of recommendation: A.

All patients admitted with severe UC require a thorough evaluation that confirms the diagnosis and rules out an enteric infection. Intravenous steroids continue to be the cornerstone of conventional therapy.[121]

Statement 3.26. Patients that do not improve with intravenous steroids within the first 72 h, confirmed through clinical, radiologic, and laboratory parameters, should be considered for surgery or second-line medical treatment. *Agreement percentage: 100%. LoE: II. Grade of recommendation: B.*

In cases of steroid-refractory disease, it is essential for alternative rescue treatment options (cyclosporine, tacrolimus, or infliximab) to be readily available early on (around the third day of steroid therapy), so that timely decisions can be made. Patients that do not respond to medical treatment have elevated morbidity when surgery is delayed.[122,123] Thus, the most important questions continue to be how to opportunely identify the patient that will need a colectomy and when to begin medical rescue therapy. The two alternatives are not mutually exclusive, and management demands careful clinical judgment.

4. Surgical treatment

Statement 4.1. UC is a chronic disease with life-threatening complications; 15-30% of patients may require surgical treatment during the course of the disease. Surgical indications are urgent or elective. *Agreement percentage: 96%. LoE: III. Grade of recommendation: C.*

Much progress has been made in the understanding of UC and in the efficacy of its different medical treatments, based on clinical practice guidelines that enable the personalized treatment of patients. Said treatment is supported by clinical, endoscopic, laboratory, and imaging monitoring that opportunely indicates the different responses to medical treatment. Despite those advances, approximately 15-30% of patients with UC will require surgical treatment at some point in the course of the disease.[124]

Depending on the clinical scenario of the patient at the time of deciding upon surgical treatment, the main indications are classified as urgent and elective. The urgent indications are medical treatment-refractory severe UC, toxic megacolon, perforation, and bleeding. The elective indications are refractoriness or adverse reactions to the different medical treatments, dysplasia or cancer, and the lack of physical development in children.[125]

Severe UC (fulminant colitis, toxic colitis) can present as the first manifestation of disease or as an exacerbation in the course of chronic disease. In addition to severe and acute inflammation of the colon, there are signs of systemic toxicity, such as fluid and electrolyte imbalance, fever, tachycardia, reduced hemoglobin, and increased ESR and CRP. Patients under those conditions must be continuously monitored to opportunely assess their response to medical treatment. If there is no early clinical response, urgent colectomy is the indicated surgical treatment.[126] Toxic megacolon is a dilation greater than 6 cm of the transverse colon with signs of systemic toxicity. It presents more frequently in patients with acute phase pancolitis, and requires monitoring with plain abdominal x-ray or CAT scan to decide on timely surgical treatment that prevents complications leading to increased postoperative morbidity and mortality, such as perforation. Perforation occurs

in approximately 2% of the patients with UC, resulting in a considerable mortality rate (27-52%). The mortality rate rises in relation to the increase in the time interval between perforation and its surgical repair. Perforation can present without dilation or marked clinical signs of peritoneal irritation, due to a reduced inflammatory response resulting from immunosuppressive therapy.[124,127] Patients that require surgical treatment should receive multidisciplinary treatment at hospitals with experience in IBD and with colorectal surgeons that more frequently perform the surgery.[128]

The main indication for elective surgery in the surgical treatment of UC is refractoriness or lack of response to medical treatment. Under such conditions, the patient does not achieve profound, sustained disease remission (with no clinical activity and with mucosal healing) and is in a chronically ill state, malnourished, immunosuppressed, incapacitated, and with poor quality of life that will lead to the development of complications if opportune surgical treatment is not carried out.[129] The presence of dysplasia and cancer are other indications for definitive, elective surgery. With the development of new endoscopic imaging technologies, supported by digital or dye-based chromoendoscopy (methylene blue or indigo carmine), plus high-definition magnification colonoscopy, greater identification of dysplasia and early cancer has been achieved.[130] Today, endoscopic treatment of dysplasia with polypectomy (lesions such as adenomas) or endoscopic mucosal resection of flat dysplasia is possible. Nevertheless, there are reports stating that such treatment has not yet been shown to be more effective than restorative proctocolectomy surgery. Opportune colectomy in pediatric patients with delayed physical growth enables practically normal development.

Statement 4.2. Patients with severe UC require early surgical assessment and should be jointly evaluated by a gastroenterologist and colorectal surgeon upon hospital admission to determine the opportune time for surgery, if required. *Agreement percentage: 96%. LoE: Va. Grade of recommendation: D.*

Severe UC is a critical life-threatening illness. Patients should always be hospitalized, with joint surveillance by a gastroenterologist and colorectal surgeon to guarantee multidisciplinary management.[125] From the time of their admission, patients should be informed of the different surgical options, if medical treatment fails. Intensive medical treatment and continuous clinical, endoscopic, laboratory, and imaging monitoring are required to opportunely determine medical treatment response. From the surgical viewpoint, fluid and electrolyte balance, nutritional support, and possibly blood transfusions, are required. Flexible sigmoidoscopy with biopsies should be performed to confirm the diagnosis and rule out enteric infections, such as cytomegalovirus, *C. difficile*, and other bacteria.[131] Plain abdominal x-ray should alert the physician to toxic dilation or perforation, and an abdominal CAT scan can be carried out in cases of doubt. When any clinical deterioration, signs of toxicity, or abdominal ''red flags'' (dilation or signs of peritoneal irritation) occur during medical therapy, colectomy with ileostomy should be considered.[132]

Statement 4.3. Immediate surgical treatment should be given to the severe UC patient with progressive deterioration that does not respond to initial intravenous therapy (3 days) or rescue therapy (7-day maximum). Morbidity and mortality are increased when there is a delayed decision to perform surgery. *Agreement percentage: 97%. LoE: II. Grade of recommendation: B.*

Approximately 27% of the patients urgently hospitalized with UC will require colectomy, due to lack of response to medical treatment or secondary to the development of complications characteristic of UC. Approximately 69% of the patients with severe UC will respond to intravenous steroids, but rescue treatment with infliximab or cyclosporine, based on the Oxford criteria, is begun in more than 56% of patients that do not respond to the intravenous steroid therapy.[133]

Both cyclosporine and anti-TNF monoclonal antibody therapy have shown a mean response time of 5 to 7 days in clinical trials.[133] Urgent colectomy should be performed in patients that continue to present with symptoms after 7 days of maximum medical treatment.[133,134] There is a greater complication rate when surgery is required in patients with second-line treatment failure that was continued for 8 days or more.[124,129,135]

Even though the colon can be saved through conservative treatment, unnecessary prolongation of medical treatment that delays surgery increases the risk for postoperative complications in immunocompromised, deteriorated, malnourished, or critically ill patients.[124,134] Postoperative mortality in those patients has been described at 0.6 to 6.9%.[133] The combination of opportune surgery and intensive medical treatment reduces the mortality rate to less than 1% in specialized centers.[136]

Statement 4.4. Colectomy with end ileostomy is the surgical procedure of choice in patients with medical treatment-refractory severe UC, severe bleeding, perforation, or toxic megacolon. A laparoscopic approach is possible in stable patients. *Agreement percentage: 97%. LoE: II. Grade of recommendation: B.*

Close to 15% of the patients with UC initially present with severe disease.[137,138] Even with the therapeutic advances made in recent decades and the reduced colectomy rate, surgery continues to play an important role in the therapeutic armamentarium of UC, given that nearly 10% of patients will require surgery during the first year of the disease,[137] and 12-25% will present with severe symptoms during the course of the illness.[138] Approximately 27% of hospitalized patients will require colectomy, due to a lack of response to medical management or because of the development of complications.[139] The colectomy rate during the first 5 years of the disease ranges from 9 to 35%, even with medical treatment.[133] Opportune surgery, together with intensive medical treatment has reduced mortality to less than 1% in specialized centers.[140]

Surgery in UC is divided into emergency/urgent and elective procedures. Emergency surgery is performed in patients that present with toxic megacolon, perforation, massive bleeding, sepsis, or fulminant disease unable to be controlled through intensive medical treatment.[134] Toxic megacolon is an acute severe disease characterized by dilation of the transverse colon > 6 cm, whose emergency management is colectomy. It occurs in 20 to 30% of patients hospitalized with severe UC. Perforation is a severe complication characterized by high mortality that varies from 27 to 57%.[129]

The emergency surgery of choice in UC is total or subtotal colectomy with end ileostomy.[138,141] In that emergency situation, the primary surgical strategy is diseased colon removal, ileostomy construction, leaving the rectum in situ, and reduced surgery duration to prevent progression to multiple organ failure and possible death.[129,139] In the hands of specialized surgeons, the procedure is quick and safe and enables later reconstruction or restoration of bowel transit.[138]

Rectal stump management is a subject of debate. Distal closure through the Hartmann procedure or the creation of a mucosal fistula have both been accepted. Extrafascial placement of the distal rectosigmoid segment may be associated with minor septic pelvic complications, but in the cases in which the rectal stump is left closed, they are prevented through transrectal drainage.[124,138] The laparoscopic approach is a reasonable alternative to open surgery, and both procedures have been shown to be equally safe. The laparoscopic approach takes longer, but its advantages are reduced postoperative pain, more rapid commencement of stoma function, and shorter hospital stay.[140] Because laparoscopy is a less traumatic approach, fewer adhesions are likely to be produced, resulting in less intestinal obstruction, which is one of the main postoperative complications in those patients.[124]

Statement 4.5. Restorative proctocolectomy with an ileoanal J-pouch has become the most commonly performed elective surgery in UC and is considered the procedure of choice. *Agreement percentage: 85%. LoE: II. Grade of recommendation: B.*

Restorative proctocolectomy with an ileoanal pouch (IAP) is currently considered the criterion standard for elective surgical treatment of UC. It has the advantage of making a permanent stoma unnecessary, preserving the natural defecation pathway. There are several controversial aspects regarding IAP formation, among which are the type of reservoir (J, S, or W), type of suturing (hand-sewn or stapled), the performance of a diverting ileostomy, and the type of surgical approach (open or laparoscopic).

Type of reservoir

IAP formation, regardless of the type, is a complex surgery and should be performed by expert colorectal surgeons. The ileoanal J-pouch is the procedure of choice, because it is the simplest to perform, compared with the other types, and all of them provide similar results.

In their meta-analysis that included 18 studies, with a total of 1,519 patients with UC and familial adenomatous polyposis (FAP), Lovegrove et al. compared the short-term and long-term results of the J-pouch (689 patients), S-pouch (524 patients), and W-pouch (306 patients). No statistically significant differences were found in relation to the total of postoperative complications, anastomosis leakage, surgical site infection, anastomosis stricture, pouchitis, or reservoir failure. The patients with the S-pouch or W-pouch had a lower number of defecations in 24 h and less necessity of using anti-diarrheal agents, compared with the J-pouch. However, J-pouch intubation is not needed to achieve defecation.[142]

Manual or mechanical reservoir

Lovegrove et al.[143] conducted a meta-analysis that included 21 studies with a total of 4,183 patients with UC and FAP that underwent IAP (2,699 hand-sewn pouches and 1,484 stapled pouches). No significant difference was found in the incidence of postoperative complications between the two groups (anastomosis leakage: 8.8% vs 5.2%, p = 0.42; fistula: 5.9% vs 2.2%, p = 0.31; pouchitis: 2.2% vs 5%, p = 0.81; stricture: 18.2% vs 12.5%, p = 0.20; pouch failure: 5.3% vs 2.3%, p = 0.06). The stapled pouch had an improved incidence of nocturnal fecal seepage and pad usage (OR: 2.78, p<0.001 and OR: 4.12, p = 0.007, respectively). There was no statistically significant difference between the frequency of defecation (p = 0.562) or the administration of anti-diarrheal agents (p = 0.422). In relation to anorectal physiology, the resting and squeezing pressure was significantly reduced in the hand-sewn pouch group by 13.4 and 14.4 mm Hg, respectively (p < 0.018). There was a greater incidence of dysplasia in the anal transition zone, but it was not statistically significant (OR: 0.42, p = 0.080).

Given the available surgical evidence, the double-stapling technique, reserving mucosectomy with hand-sewn anastomosis for patients with rectal high-grade dysplasia, is recommended.

Diverting ileostomy

IAP can be carried out in one, two, or three stages. One-stage surgery consists of forming the pouch with no diverting ileostomy to avoid a second surgery and the consequent morbidity and mortality, as well as the adverse effects associated with the stoma. In two-stage surgery, the pouch is formed, leaving a diverting ileostomy in the segment, to be closed at least 3 months after the first surgery and after examination and ruling out of pouch leaks or fistula. Three-stage surgery consists of performing subtotal colectomy with end ileostomy, after which the IAP is formed with a protective stoma, closing the ileostomy in a third surgical time. That procedure has been reserved almost exclusively for urgent surgery.

In their meta-analysis, Weston-Petrides et al.[144] included a total of 1,486 patients in 17 comparative studies (765 with no ileostomy and 721 with ileostomy). The development of leakage associated with the pouch was significantly higher

in the group with no stoma (OR: 2.37; p = 0.002). On the other hand, the development of anastomosis stricture (OR: 0.31; p = 0.045) and pouch failure (OR: 0.30; p = 0.009) was significantly lower in the group with no stoma. Bowel obstruction was more common in the group with stoma (OR: 2.37; p=0.002).

Even though one-stage surgery in selected cases (patients with good nutritional status, young patients, steroid-free patients, tension-free anastomosis with adequate irrigation) has been proposed in some studies, two-stage surgery is the prevailing technique that is currently in use. It is rare for patients with UC that are candidates for surgery not to have anastomosis leakage risk factors, and the two-stage surgery attempts to reduce septic complications associated with leakage or pouch dehiscence.

Statement 4.6. Proctocolectomy with definitive ileostomy is the treatment of choice for UC patients that are not candidates for restorative proctocolectomy. *Agreement percentage: 97%. LoE: II. Grade of recommendation: B.*

Proctocolectomy with definitive ileostomy is considered safe, effective, and potentially curative for patients with UC, and is the traditional surgical approach. It is the first-line surgical treatment in patients that are not candidates for restorative surgery and in patients with a high probability of pouch failure. It can also be performed in patients programmed for IAP in whom the pouch cannot be made due to consequent anatomic circumstances, such as the length of the mesentery.

The patients that are candidates for proctocolectomy with definitive ileostomy are those with sphincteric complex lesion, significant previous anoperineal disease, and low physiologic reserve secondary to other comorbidities.[124] We recommend the routine ordering of anorectal physiology tests, such as anal manometry and pudendal motor nerve terminal latency before making a surgical decision.

Although there are no prospective studies that compare conventional proctectomy (extrasphincteric) with the intersphincteric procedure, it is logical to suppose that intersphincteric dissection results in a smaller wound with less probability of wound-associated complications (dehiscence, hematoma, infection, or perineal hernia). In addition, because it is a benign pathology, the authors recommend intersphincteric proctectomy performed by a colorectal surgeon that has mastered the procedure.

Complications related to this type of surgery include stricture or prolapse of the stoma, bowel obstruction, surgical site infection, fistula, persistent pain, delayed perineal wound healing, sexual dysfunction, bladder dysfunction, and infertility. The main advantage of proctocolectomy with definitive ileostomy over IAP is that it prevents the risk for pouchitis, while offering quality of life comparable to that obtained with the pouch.[145]

It is mandatory to clearly and thoroughly inform the patient of the implications, risks, and benefits of each of the surgical alternatives described above, to make a responsible and shared decision in accordance with his or her preferences and expectations.

Statement 4.7. Colectomy with ileorectal anastomosis may be performed in a group of highly selected patients, as an alternative to the ileoanal pouch. *Agreement percentage: 100%. LoE: II. Grade of recommendation: B.*

Colectomy with ileorectal anastomosis should be considered only when rectal inflammation is mild and has been well controlled with suppositories or mesalazine enemas during the course of the disease.[146–150] It is important to clinically and manometrically confirm that the distensibility of the rectum is conserved, the patient is continent, and there are no signs of malignant changes in the colon or rectum.[151,152] The rectum must be capable of acting as a reservoir. Said procedure should be considered if, at endoscopy, the mucosa is relatively conserved and there is distensibility of the wall upon air insufflation, if proctography reveals similar data, if manometry is normal (or almost normal), which is synonymous with anal continence, and if there is no dysplasia.[153,154] Unfortunately, not many patients meet those conditions. The presence of a contracted rectum that does not carry out its function as a reservoir is a contraindication for colectomy with ileorectal anastomosis. Therefore, the appropriate candidates for the procedure are patients that have mild rectal disease, adequate distensibility at lower endoscopy, and with low risk for developing rectal cancer.[146,149,152,154–158] Elderly patients with short disease duration can also be good candidates, as well as young patients that wish to avoid the potential risk of sexual dysfunction and infertility associated with pelvic dissection, and those patients that wish to return to normal activities as soon as possible.

The patient should be prepared for close follow-up, due to the risk for malignancy in the remaining rectal mucosa. Annual rectoscopy with biopsies analyzed by an expert gastrointestinal pathologist is required. If that is not possible, then said technique should not be suggested.

In the past, before the introduction of restorative proctocolectomy, colectomy with ileorectal anastomosis was carried out in 10 to 90% of patients. That wide range was the consequence of preferences and prejudices on the part of the surgeons. With the advent of restorative proctocolectomy, the frequency of colectomy with ileorectal anastomosis has gradually decreased. Nevertheless, it continues to have a place in the treatment of UC, given that it is technically easy to perform, has few complications, and provides satisfactory long-term results in well-selected cases.

Statement 4.8. Minimally invasive surgery is safe and feasible for elective UC treatment and has both short-term and long-term advantages. The laparoscopic approach should be performed in centers with experience in the procedure. *Agreement percentage: 94%. LoE: III. Grade of recommendation: C.*

A large number of patients with UC (20%) still require surgical procedures, despite the advent of new medical and biologic therapies.[159] Surgical indications in UC can be elective (refractory chronic UC and dysplasia/cancer) or urgent (acute severe UC).

In 1978, Parks and Nicholls[160] described restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA). It is the treatment of choice for patients with UC that require elective surgery.[160] The 2015 ECCO guidelines for the surgical treatment of UC recommend the J-pouch as standard treatment, because of its simplicity and good long-term results.[125]

However, it has a high complication rate. The risk for infertility is three-fold greater with the open surgical technique than with laparoscopy. Minimally invasive laparoscopic surgery has significantly reduced the percentage of infertility.[161,162]

Surgery of the colon and rectum in UC is currently divided into pure laparoscopic surgery and hand-assisted laparoscopic surgery (HALS).[163]

There are only two controlled clinical trials that compare laparoscopic surgery with open surgery for the treatment of UC. In the first study, Maartense et al.[164] included 30 patients that underwent the hand-assisted procedure (HALS) versus 30 patients that underwent open surgery. The data were obtained within the time frame of 2000-2003. The following statistically significant differences were reported: longer surgery duration and better cosmetic results with laparoscopy. There were no statistical differences in morbidity, mortality, or hospital stay between the two groups. Laparoscopy was the more expensive procedure. No cases of conversion were described.

In 2013, Schiessling et al.[165] compared 5-port laparoscopy (21 patients) vs open surgery (21 patients) and concluded that the laparoscopic performance of restorative proctocolectomy was feasible. They found longer surgery duration in open procedures, better cosmetic results with laparoscopy, and no statistically significant differences in relation to blood loss, hospital stay, bowel function recovery, or quality of life.[165]

The Cochrane study contained an analysis comparing laparoscopic IPAA vs open IPAA in patients with UC and familial adenomatous polyposis. The authors concluded that laparoscopic IPAA was safe and feasible in centers with experience and offered limited short-term advantages that included better postoperative recovery. There were no differences between open IPAA vs laparoscopic IPAA regarding frequency of defecation, fecal incontinence, and sexual function.[166]

The usefulness of laparoscopic surgery in episodes of severe UC has also been analyzed. Total colectomy with ileostomy and rectal mucous fistula is required in those patients and they generally need a second procedure (two-stage surgery). The feasibility and safety of laparoscopic surgery in urgent severe episodes have been evaluated in studies with good results. Dunker et al.[167] retrospectively compared open surgery versus laparoscopy in 42 patients with severe UC that underwent total colectomy with rectal mucous fistula and ileostomy and reported that laparoscopic surgery was safe and feasible in those settings.

Bartels et al.[168] conducted a systematic review and meta-analysis in the scenario of severe UC with a total of 966 patients. Despite the fact that the studies analyzed were retrospective, the rates of wound infection and intra-abdominal abscess were significantly lower in the patients that underwent laparoscopic surgery.

Another advantage of laparoscopic surgery is related to fertility. It has been concluded in several meta-analyses that the risk for infertility increases three-fold with open IPAA. The risk for altering fertility is thought to decrease with the performance of laparoscopic surgery because fewer adhesions (Fallopian tube and pelvic cavity adhesions) develop and the incisions are smaller.[162]

The 2015 ECCO guidelines state that laparoscopic surgery is safe and feasible for elective surgical treatment of UC and offers better short-term results, with the exception of longer surgery duration and higher cost. The long-term advantages are the formation of fewer adhesions with preserved fertility and a lower incidence of hernias.[125]

Statement 4.9. Restorative proctocolectomy is the procedure of choice in patients with carcinoma or multifocal high-grade or low-grade dysplasia. *Agreement percentage: 96%. LoE: II. Grade of recommendation: B.*

The incidence of colorectal cancer (CRC) in patients with IBD reported in the most recent meta-analyses of population cohorts is 1, 2, and 5% after 10, 20, and over 20 years of disease duration.[169] The reduction in incidence is due to the implementation of endoscopic surveillance programs through new techniques of colonoscopy with targeted biopsy and resection of suspicious lesions, when possible.

Chronic inflammation of the mucosa is a key factor in carcinogenesis in patients with IBD.[170] The main risk factors associated with the development of malignancy include disease extension (pancolitis), disease duration (more than 8 years), disease diagnosis at an early age, family history of IBD or CRC, and concomitant primary sclerosing cholangitis.[124]

Dysplasia is the best risk marker for colorectal cancer in IBD. Carcinogenesis in IBD follows the sequential inflammation progression from low-grade dysplasia (LGD) to high-grade dysplasia (HGD) to CRC. However, CRC can occur in a patient with no history of dysplasia, and not all patients with LGD develop CRC by way of HGD.[170] Therefore, LGD can be considered the definitive point of intervention at which prophylactic colectomy for CRC in patients with UC should be performed.[171] It is estimated in the most recent systematic reviews that LGD confers a 9% risk for CRC and a 12% risk for HGD. In a meta-analysis by Murphy et al.,[172] they observed that dysplasia was associated with a low incidence of negative lymph nodes, if surgery was postponed up to 5 years.

The guidelines of the International Consensus on Surveillance and Management of Dysplasia in IBD have very recently been published. They state that surveillance with colonoscopy, rather than surgery, is indicated after complete endoscopic removal of a dysplastic polypoid lesion. Their recommendation is the same for visible, non-polypoid dysplastic lesions completely resected through advanced

endoscopic techniques. Colectomy is reserved for cases of invisible high-grade dysplasia, due to the high risk for CRC.[67]

The finding of colorectal cancer, non-adenoma-like dysplasia-associated lesion or mass (DALM), or LGD has been accepted as the main indication for proctocolectomy with or without anastomosis (ileal pouch-anal anastomosis), given that there is concomitant malignancy at the time of colectomy in approximately 43 to 50% of cases. The management of lesions with flat, unifocal LGD is a subject of debate, with both endoscopic surveillance and total proctocolectomy being suggested. The decision should be made with the patient, explaining the risks involved in endoscopic surveillance versus those of surgery and the possible development of HGD or CRC.[124]

Restorative proctocolectomy with ileal pouch-anal anastomosis (RPC-IPAA) is the standard procedure in patients with UC. The rectal mucosa is completely resected, thus eliminating the risk for the future development of carcinoma in the rectal remnant. Colectomy in patients with dysplasia or carcinoma, requires sufficient lymph node resection with mobilization of the mesentery and high vascular ligature.[173]

Statement 4.10. Surveillance or follow-up of the ileo-anal pouch is not necessary in the asymptomatic patient, unless there are risk factors, such as a history of neoplasia or primary sclerosing cholangitis. *Agreement percentage: 97%. LoE: III. Grade of recommendation: C.*

In general, the follow-up of patients with ileo-anal pouch is controversial. There is no evidence suggesting that the lack of follow-up results in any risk for the patient, except the debatable risk for cancer. Follow-up should be individualized in accordance with the characteristics of each patient. No specific follow-up protocol is required in asymptomatic patients with no risk factors (history of neoplasia or primary sclerosing cholangitis).[125] Pouch follow-up is recommended in symptomatic patients. Clinical signs and symptoms of inflammation of the ileo-anal pouch, such as an increased number of defecations, the presence of mucus and blood, tenesmus, fever, or pelvic pain, should alert the physician to perform diagnostic and treatment follow-up. The presence of symptoms related to pouch complications, such as incontinence or obstructive signs, or perianal alterations, such as the presence of fistulas or stricture, also requires diagnostic follow-up carried out by experienced specialists, for successful diagnosis and treatment.[174]

There is not enough evidence available to make recommendations about ileo-anal pouch surveillance, with respect to malignant changes. However, high-risk patients, such as those with primary sclerosing cholangitis, a rectal remnant longer than 2 cm, type C mucosa (permanent mucosal atrophy and severe inflammation), or previous malignancy or dysplasia should have long-term follow-up for dysplasia surveillance of the pouch or rectal remnant.[131] Approximately 30 pouch cancers have been reported, all of them in patients that were operated on for dysplasia or cancer in the surgical specimen of the first surgery. Despite their small number, attention must be focused on those high-risk patients.[175]

In a systematic review of dysplasia or cancer after restorative proctocolectomy, even when the surgical indication had been for dysplasia or cancer, the risk for newly developing dysplasia or cancer in the rectal remnant or pouch was very low. The prevalence of high-grade dysplasia, low-grade dysplasia, or undefined dysplasia was 0.15 (range: 0.4-49), 0.98 (range: 0-15.62) and 1.23% (range: 0-25.28%), respectively.[176] Dysplasia was equally frequent in the pouch, rectal remnant, or anal transition zone. Dysplasia diagnosed before or during surgery appears to be a significant predictor for the development of dysplasia in the pouch.[177]

Annual surveillance in high-risk patients and every 5 years in low-risk patients appears to be reasonable.[178]

Statement 4.11. Early endoscopic revision of the reservoir is recommended in symptomatic patients to identify pouchitis (inflammation of the reservoir), cuffitis (inflammatory disease activity in the rectal remnant), and other added alterations. *Agreement percentage: 97%. LoE: III. Grade of recommendation: C.*

Pouchitis (pouch inflammation) is the most common complication and occurs in more than 50% of patients at 10 years. Extensive UC, the presence of extraintestinal manifestations, mainly primary sclerosing cholangitis, being a nonsmoker, high preoperative levels of p-ANCA, and steroid and NSAID use are considered risk factors for developing pouchitis.[46]

The clinical diagnosis of pouchitis is made when there is an increase in the number of defecations, urgency, abdominal cramps, and incontinence. Nevertheless, diagnosis is not simple. It requires the combined evaluation of symptoms, endoscopic findings, and histologic characteristics.[179] The most frequently used method for the diagnosis and classification of pouchitis is the 18-point Pouchitis Activity Index, based on the evaluation of symptoms, endoscopy, and histology. Diagnosis is made through the index when there are clinical symptoms of diarrhea > 6 defecations/day, endoscopic findings > 4 signs (edema, granularity, friability, loss of submucosal vascular pattern, bleeding or ulceration), and histopathologic alterations: a minimum score of 4 on a 6-point index (polymorphic nuclear leukocyte infiltration and percentage of ulceration in a low power field).[180] Endoscopy is the best method for diagnosing pouchitis and differentiating other pathologies, such as cuffitis (active inflammation of the rectal remnant), stricture, anastomosis leakage, ischemia, irritable pouch syndrome, fistulas and abscesses, Crohn's disease, cytomegalovirus, *C. difficile*, dysplasia, and cancer.[181,182]

Statement 4.12. First-line treatment in patients with acute pouchitis is 500 mg of ciprofloxacin twice a day or 15-20 mg/kg/day of metronidazole for 2 weeks. *Agreement percentage: 96%. LoE: II. Grade of recommendation: B.*

Acute pouchitis in its initial stages responds well to antibiotic therapy. Surgical complications, such as anastomosis leakage or fistula, should be suspected in patients

with symptoms of pouchitis immediately after the construction of the reservoir and closure of the diverting ileostomy, and in patients that do not respond to antibiotic therapy. Few randomized, placebo-controlled trials on the treatment and prevention of pouchitis have been published. In clinical practice, metronidazole, ciprofloxacin, tinidazole, and rifaximin have been used in the treatment of acute pouchitis.[183,184] First-line therapy includes a regimen of 14 days of metronidazole (15-20 mg/kg/day) or ciprofloxacin (1 g/day). Side effects are less frequent with ciprofloxacin. Other antibiotics have been studied and proved to be effective in some patients in small studies, and they include tinidazole, rifaximin, and amoxicillin-clavulanic acid.[185]

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Conflict of interest

Jesús K. Yamamoto-Furusho has received professional fees from Abbvie, Takeda, Janssen, UCB, Almirall, Pfizer, Novartis, and Danone as a Speaker, Key Opinion Leader, and member of national and international advisory boards. He has received research funding from Bristol, Shire, and Pfizer and is president of the Pan American Crohn's and Colitis Organisation (PANCCO).

Francisco Bosques-Padilla has been a Speaker and Advisor for Abbvie, Janssen, Takeda, and Ferring.

The remaining co-authors declare they have no conflict of interest.

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