Revista de Gastroenterología de México 87 (2022) 342–361

REVISTA DE GASTROENTEROLOGÍA DE MÉXICO

www.elsevier.es/rgmx

REVIEW ARTICLE

Update of the PANCCO clinical practice guidelines for the treatment of ulcerative colitis in the adult population☆

F. Juliao-Baños[a,*], C.F. Grillo-Ardila[b], I. Alfaro[c], M.T. Andara-Ramírez[d], O. Avelar-Escobar[e], J. Barahona-Garrido[f], S. Bautista-Martínez[g], F.J. Bosques-Padilla[h], J.A. De Paula[i], K. Ernest-Suárez[j], M.T. Galiano[k], B. Iade-Vergara[l], Patricio-Ibañez[m], M.L. Jara-Alba[n], P.G. Kotze[o], M.C. Miranda-Ojeda[p], R. Ortuño-Escalante[q], G. Otoya- Moreno[r], F.N. Piñol-Jiménez[s], I.C. Ramos-Polo[t], A. Sambuelli[u], M. Toro[v], E.A. Torres[w], G.R. Veitia-Velásquez[x], J.K. Yamamoto-Furusho[y], C. Zaltman[z], F. Steinwurz[aa], M. Vallejo-Ortega[ab], J.I. Torres-Castillo[ac], C. Hamon-Pinilla[ad], C.H. Calderon-Franco[ae], A.M. Escobar-Villegas[af], Developer group

[a] *Clínica de Enfermedad Inflamatoria Intestinal, Unidad de Gastroenterología, Hospital Pablo Tobón Uribe, Medellín, Colombia*
[b] *Departamento de Ginecología y Obstetricia, Universidad Nacional de Colombia; Grupo de Investigación Clínica y Epidemiológica del Cáncer, Instituto Nacional de Cancerología, Bogotá, Colombia*
[c] *Servicio Medicina Interna Hospital Regional de Concepción, Departamento de Medicina Interna, Universidad de Concepción, Concepción, Chile*
[d] *Servicio de Gastroenterología, Instituto Hondureño de Seguridad Social, Tegucigalpa, Honduras*
[e] *Servicio de Gastroenterología, Instituto Salvadoreño del Seguro Social, San Salvador. El Salvador*
[f] *Servicio de Gastroenterología, Enfermedades Digestivas de Guatemala, Ciudad de Guatemala, Guatemala*
[g] *CEDIMAT Plaza de la salud, Departamento Gastroenterología, Clínica EII, Santo Domingo, Dominican Republic*
[h] *Servicio de Gastroenterología, Hospital Universitario Dr. José Eleuterio González, Universidad Autónoma de Nuevo León (UANL), Monterrey, Nuevo León, Mexico*
[i] *Servicio de Gastroenterología del Hospital Italiano de Buenos Aires, Equipo de Enfermedades Inflamatorias del Intestinales del Servicio de Gastroenterología del Hospital Italiano de Buenos Aires, Buenos Aires, Argentina*
[j] *Servicio de Gastroenterología y Endoscopía Digestiva, Hospital México, Caja Costarricense de Seguro Social, Escuela de Medicina de la Universidad de Costa Rica, San José, Costa Rica*
[k] *Gastroenteróloga y Endoscopista Gastrointestinal, Clínica de Marly, Bogotá, Colombia*
[l] *Departamento de Gastroenterología de CASMU, Asociación de Crohn's y Colitis Uruguay (ACCU), ECCO y PANCCO, Montevideo, Uruguay*
[m] *Programa Enfermedad Inflamatoria Intestinal, Departamento de Gastroenterología, Clínica Las Condes, Facultad de Medicina Universidad de Chile, Campus CLC, Santiago de Chile, Chile*

☆ Please cite this article as: Juliao-Baños F, Grillo-Ardila CF, Alfaro I, Andara-Ramírez MT, Avelar-Escobar O, Barahona-Garrido J, et al. Actualización de la guía de práctica clínica PANCCO para el tratamiento de la colitis ulcerativa en población adulta, Revista de Gastroenterología de México. 2022;87:342–361.

* Corresponding author. Tel.: +3153960499.
E-mail address: fabianjuliao@hotmail.com (F. Juliao-Baños).

[n] *Grupo Ecuatoriano de Estudio de Enfermedad Inflamatoria Intestinal, Hospital Teodoro Maldonado Carbo, Clínica de Enfermedad Inflamatoria Intestinal, Hospital Teodoro Maldonado Carbo, Guayaquil, Ecuador*
[o] *Profesor Asistente de Cirugía, Clínica de Enfermedad Inflamatoria Intestinal, Universidad Católica de Paraná, Curitiba, Brazil*
[p] *Servicio de Gastroenterología, Hospital de Clínicas, San Lorenzo, Paraguay*
[q] *Instituto de Gastroenterología Boliviano-Japonés, Ciudad de la Paz, Bolivia*
[r] *Servicio de Gastroenterología Hospital Nacional Güillermo Almenara I;· Lima, Peru*
[s] *Sociedad Cubana de Gastroenterología, Centro Nacional de Cirugía de Mínimo Acceso (CNCMA), La Habana, Cuba*
[t] *Servicio y de la Unidad de Endoscopia del Complejo Hospitalario Metropolitano Dr. Arnulfo Arias Madrid, Clínica Hospital San Fernando, Ciudad de Panamá, Panama*
[u] *Sección de Enfermedades Inflamatorias Intestinales, Hospital Bonorino Udaondo, Buenos Aires, Argentina*
[v] *Gastroenterología y Endoscopía Digestiva, Grupo de Trabajo en Enfermedades Inflamatorias Intestinales de Clínica HIGEA, Mendoza, Argentina*
[w] *Departamento de Medicina, Escuela de Medicina de la Universidad de Puerto Rico (UPR), Unidad de Investigación en Gastroenterología, Centro para Enfermedades Inflamatorias del Intestino, UPR, San Juan, Puerto Rico*
[x] *Servicio de Gastroenterología, Hospital Vargas de Caracas, Caracas, Venezuela*
[y] *Clínica de Enfermedad Inflamatoria Intestinal (EII), Departamento de Gastroenterología, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico*
[z] *Departamento de Clínica Médica, Universidad de Federal do Rio de Janeiro, Ambulatorio de Doença Inflamatoria Intestinal, HUCFF-UFRJ, Río de Janeiro, Brazil*
[aa] *Gastroenterólogo del Hospital israelita Albert Einstein, São Paulo, Brazil*
[ab] *Instituto de Investigaciones, Universidad Nacional de Colombia, Grupo de Investigación Clínica y Epidemiológica del Cáncer, Instituto Nacional de Cancerología, Bogotá, Colombia*
[ac] *Servicio de Medicina de Emergencias, Facultad de Medicina, Universidad Nacional de Colombia, Bogotá, Colombia*
[ad] *Departamento de Ginecología y Obstetricia, Facultad de Medicina, Universidad Nacional de Colombia, Bogotá, Colombia*
[ae] *Departamento de Medicina Interna, Facultad de Medicina, Universidad El Bosque, Bogotá, Colombia*
[af] *Representante de pacientes con Colitis Ulcerativa, Medellín, Colombia*

Received 6 February 2022; accepted 6 April 2022
Available online 22 July 2022

KEYWORDS
Ulcerative colitis;
Treatment;
Inflammatory bowel disease;
Mucosal healing;
Biologic therapy

Abstract: Ulcerative colitis (US) is a chronic disease of unknown etiology. It is incurable and its clinical course is intermittent, characterized by periods of remission and relapse. The prevalence and incidence of the disease has been increasing worldwide. The update presented herein includes the participation of healthcare professionals, decision-makers, and a representative of the patients, all of whom declared their conflicts of interest. Answerable clinical questions were formulated, and the outcomes were graded. The information search was conducted on the Medline/PubMed, Embase, Epistemonikos, and LILACS databases, and covered grey literature sources, as well. The search was updated on November 30, 2020, with no restrictions regarding date or language. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) classification system was implemented to establish the strength of the recommendation and quality of evidence. A formal consensus was developed, based on the RAND/UCLA methodology and the document was peer reviewed. The short version of the Clinical Practice Guidelines for the Treatment of Ulcerative Colitis in the Adult Population is presented herein, together with the supporting evidence and respective recommendations. In mild-to-moderate UC, budesonide MMX is an option when treatment with 5-ASA fails, and before using systemic steroids. In moderate-to-severe UC, infliximab, adalimumab, vedolizumab, ustekinumab, and tofacitinib can be used as first-line therapy. If there is anti-TNF therapy failure, ustekinumab and tofacitinib provide the best results. In patients with antibiotic-refractory pouchitis, anti-TNFs are the treatment of choice.

PALABRAS CLAVE
Colitis ulcerativa;
Tratamiento;
Enfermedad inflamatoria intestinal;
Cicatrización mucosa;
Terapia biológica

Actualización de la guía de práctica clínica PANCCO para el tratamiento de la colitis ulcerativa en población adulta

Resumen La colitis ulcerativa (CU) es una enfermedad crónica de etiología desconocida, incurable, su curso clínico es intermitente, caracterizado por periodos de remisión y recaídas, su prevalencia e incidencia mundial ha venido incrementando. En esta actualización participaron profesionales de la salud, tomadores decisiones y un representante de los pacientes. Todos los involucrados declararon sus conflictos de interés. Se formularon preguntas clínicas contestables y se graduaron los desenlaces. La pesquisa de la información se realizó en Medline/PubMed, Embase, Epistemonikos y LILACS. La búsqueda también abarcó fuentes de literatura gris y se actualizó el 30 de noviembre de 2020 sin restricciones por fecha o idioma. Se implementó la aproximación GRADE (Grading of Recommendations Assessment, Development and Evaluation) para establecer la calidad de la evidencia y la fuerza de las recomendación. Se realizó consenso formal implementando la metodología RAND/UCLA. El documento fue objeto de revisión por pares. Se presenta aquí la versión corta de La Guía de Práctica Clínica para el Tratamiento de la Colitis Ulcerativa en Población Adulta, junto con la evidencia de apoyo y las recomendaciones respectivas. En CU leve a moderada, la budesonida MMX es una opción en caso de falla a 5-ASA, y antes de usar esteroides sistémicos. En colitis ulcerativa moderada a severa, infliximab y adalimumab, vedolizumab, ustekinumab y tofacitinib pueden ser usado como terapia de primera línea. En caso de falla a anti-TNFs, los mejores resultados son con ustekinumab y tofacitinib. En pacientes con reservoritis refractaria a antibióticos, el tratamiento de elección son los anti-TNFs.

Introduction

Ulcerative colitis (UC) is a chronic idiopathic inflammatory disease that almost always affects the rectum and can extend to involve the entire colon. Its most frequent symptoms are bloody diarrhea, associated with urgency and rectal tenesmus.[1] Its clinical course varies, with more activity at disease onset and after diagnosis, then followed by remission.[2] Since its first description in 1859 in London, by Sir Samuel Wilks, its prevalence and incidence have been increasing worldwide, like those of other immunologic diseases.[3] Recent studies have shown that Latin America is no exception, and UC is the most frequent type of inflammatory bowel disease (IBD).[4–6]

To diagnose the patient with UC, the clinical history, physical examination, endoscopic findings, laboratory tests, and histopathologic alterations must be considered, ruling out an infectious etiology of the colitis in all cases.[1] The Montreal classification was created by expert consensus in 2005, and classifies UC according to extension and activity.[7] The American College of Gastroenterology proposed a new classification of UC, modifying the traditional Truelove and Witts classification by adding fecal urgency, the C-reactive protein and fecal calprotectin biomarkers, and endoscopic severity, which is necessary for defining the therapeutic goals.[8] Despite the fact that there are established diagnostic criteria, a considerable percentage of patients are diagnosed late,[6] favoring disease progression. Numerous studies have shown that UC has a negative impact on quality of life, seriously affecting the work performance and health conditions of those patients.[9] In addition, 10–21% of patients with UC will require hospitalization, one to five years after diagnosis.[10]

Treatment is carried out through pharmacologic interventions, with refractory cases requiring surgery. Studies have shown that risk increases over time, and around 10–15% of patients will require colectomy after 10 years with the disease.[11] New treatments, such as biosimilars, new biologics, and small-molecule drugs, have recently emerged.

In 2017, the Pan American Crohn's and Colitis Organisation (PANCCO) published its first consensus on the diagnosis and treatment of UC. Since then, new concepts of long-term treatment goals have appeared, such as mucosal and histologic healing,[12] along with new pharmacologic (budesonide MMX, biosimilars, biologic therapies, and small-molecule drugs) and non-pharmacologic (diet, fecal microbiota transplant, cannabis, and turmeric, among others) therapeutic alternatives.

Given the above, carrying out clinical practice guidelines providing evidence-based information focused on the treatment of UC in adult patients was considered necessary, to establish recommendations in the management of the disease in the Latin American context.

Materials and methods

For the updating of these guidelines, the developer group (DG) was made up of gastroenterology internists, gastroenterology surgeons, and coloproctologists.[13,14] Likewise, experts in clinical epidemiology participated in the process, supporting the collection, evaluation, and synthesis of the evidence through a systematic search of the literature. The DG was also supported by a representative of the patients (a patient herself), who provided her perspective[13,14] during each of the critical stages of the process (scope and goal

formulation, PICO question draft, outcome grade, evidence analysis, and recommendation creation).

All members provided written conflict of interest statements,[15] which are available on the website of the managing body (PANCCO). The PANCCO was also the funding body present throughout the process, to ensure the transferability and applicability of the document's content to the Latin American context. The funding body had no influence on the guideline recommendations.[13,14]

The scope and goals of the guidelines were defined through mutual agreement between the managing body and the DG.[13] The aim of the present initiative was to serve as a guide in managing patients above 15 years of age, diagnosed with UC, regardless of disease activity or extension, that require treatment for the induction and maintenance of remission or for pouchitis. These guidelines were not directed at the pregnant population, patients with Crohn's disease, or patients with extraintestinal complications of colitis, nor do they cover the management of treatment-associated adverse effects, the care of patients with infectious colitis, or aspects related to the diagnosis, prognosis, or rehabilitation of the patients with UC.

Once the scope and goals of the guidelines were defined,[13] the list of general questions was placed in the PICO format, prioritizing feasibility, relevance, and the presence of unjustified variability, according to the availability of new evidence.[13] The outcomes were graded in relation to their relevance, following the GRADE methodology,[13] which sets forth that the importance of each result varies according to the culture and perspective of the system actors.[16] To identify the available evidence, the process of a systematic search of the literature was started, following the directives proposed by the Cochrane Collaboration.[16] To do so, the DG had the support of an information search expert trained by the Cochrane group, who, together with the clinical experts, identified the terms in both free and controlled language[13] that reflected the key components of each investigation question.[17] The information expert, utilizing Boolean operators, connectors, truncation, and highly sensitive filters, then designed the search strategy, whose face validity was determined by one of the leaders of the guidelines,[13] to lastly be carried out on MEDLINE, Embase, and the Cochrane Library databases.

The search was updated on November 30, 2020, unrestricted by language or date,[13] and was also extended to other sources of information, such as contact with experts and the ''snowballing'' method of review and reading of the references included.[17] To answer the formulated questions, the inclusion of systematic reviews with meta-analyses was prioritized, and when necessary, the primary studies were identified and retrieved for the guidelines.[13] The group of clinical and methodological experts participated in the selection of the studies to be included, following the inclusion and exclusion criteria (characteristics of the target population, intervention, and type of study) and separately reading the titles and abstracts.[13] Discrepancies were resolved through consensus, and whenever necessary, the complete text of the document was reviewed, to minimize the possibility of excluding relevant studies.[14]

Regarding the systematic reviews, the AMSTAR-2[18] tool was utilized as a critical evaluation instrument, and the primary studies were evaluated by implementing the Risk of Bias Tool, suggested by the Cochrane Group.[19] The synthesis of the evidence was carried out, using the GRADEpro GDT App (McMaster University and Evidence Prime, Canada),[20] through which the respective evidence profiles were produced, establishing the confidence in the estimates of effect, according to high (⊕⊕⊕⊕), moderate (⊕⊕⊕◯), low (⊕⊕◯◯) or very low (⊕◯◯◯) levels of overall quality.[21] According to the GRADE methodology,[22] in principle, controlled clinical trials are high quality, but the confidence in the effect (quality) can be affected by limitations in the study design or its conduction (risk of bias), result consistency, evidence applicability, result accuracy, and lastly, publication bias.[17]

To formulate the recommendations, the evidence tables were presented during the meeting of the experts participating in the consensus, to create the guideline recommendations.[13] During that work session, each profile, together with its respective synthesis of evidence, was presented to the group of clinical and methodological experts and the patient representative.[13] They then determined the strength and direction of each recommendation, utilizing the GRADE methodology,[13] grading the quality of evidence, risk-benefit balance, costs, and patient preferences, as the primary input for defining the strength and direction of the recommendations.[13] During the meeting of the consensus participants, good clinical practice points were also formulated for circumstances in which the implementation of different options would not be reasonable.[15]

Before its submission for publication, the present guidelines underwent external peer review, by individuals with no relation to the process or the managing body.[13] They reviewed the content of the consensus and commented on the breadth and accuracy of the evidence supporting each recommendation.[14] The recommendations of the present guidelines should be updated in the next three years, or sooner, if new evidence is produced that would modify those appearing herein. Future changes should be made by an expert panel.

Results

A synthesis of the evidence and recommendations according to each question developed for the consensus follows below.

Question: What is the safety and effectiveness of pharmacologic and non-pharmacologic interventions that enable the induction of remission in patients with UC?

Recommendation No. 1: Management with topical rectal aminosalicylates is recommended for inducing clinical remission in patients presenting with ulcerative proctitis. Strong, in favor of the strategy. Quality of evidence ⊕⊕◯◯.

Good practice point: The dose of topical aminosalicylates for inducing remission should be 1 g/day.

Good practice point: Topical steroids can be used as second-line therapy for inducing remission in patients presenting with mild-to-moderate ulcerative proctitis that have therapeutic failure or intolerance to the administration of topical aminosalicylic acid.

Rectal 5-aminosalicylates for inducing remission

A systematic review[23] evaluated the effectiveness of rectal 5-aminosalicylic acid (5-ASA) administration for inducing remission in patients presenting with proctosigmoiditis with mild-to-moderate activity.

Rectal 5-aminosalicylates vs. placebo

Eight studies, including 812 participants, analyzed the comparison. The patients assigned to receive rectal 5-ASA administration had a higher frequency of remission (odds ratio [OR] 8.30; 95% confidence interval [CI] 4.28–16.12), symptom improvement (OR 8.87; 95% CI 5.30–14.83), and endoscopic improvement (OR 11.80; 95% CI 5.99–20.88).

Rectal 5-aminosalicylates vs. rectal steroids

Nine studies that included 943 participants analyzed the comparison. Rectal 5-ASA administration was associated with a higher frequency of remission (OR 1.65; 95% CI 1.11–2.45) and symptom improvement (OR 1.58; 95% CI 1.15–2.11).

Rectal 5-aminosalicylates vs. oral 5-aminosalicylates

Four studies on a total of 214 participants analyzed the comparison. Therapy with rectal 5-ASA was not associated with a higher or lower frequency of symptom improvement (OR 2.25; 95% CI 0.56–9.54) or of patients that achieved remission (OR 1.45; 95% CI 0.41–5.10).

Recommendation No. 2: Management with oral aminosalicylates is recommended for inducing clinical and endoscopic remission in patients with left-sided or extensive UC with mild-to-moderate activity. Strong, in favor of the strategy. Quality of evidence ⊕⊕◯◯.

Good practice point: The response to treatment with aminosalicylates should be evaluated at four to eight weeks of treatment. The need to modify the therapy should be defined if there is treatment failure.

Good practice point: The dose of oral aminosalicylates for inducing remission should be at least 2.4 g/day, and in some cases, ≥3 g/day can be used.

Good practice point: To improve treatment adherence, a formulation that enables one aminosalicylate dose daily is preferred, if available.

Oral 5-aminosalicylates for inducing remission

A systematic review[24] evaluated the effectiveness of oral 5-ASA administration for inducing remission in patients with mild-to-moderate recurrent or recently diagnosed UC.

Oral 5-aminosalicylates vs. placebo

Twenty-one studies that included 2,256 participants analyzed the comparison. The patients assigned to the oral 5-ASA group had a lower frequency of failure to induce remission (relative risk [RR] 0.86, 95% CI 0.82—0.89), clinical response (RR 0.68, 95% CI 0.61—0.75), or endoscopic response (RR 0.77, 95% CI 0.67—0.89), with no differences in serious adverse events (RR 0.53, 95% CI 0.18–1.56). The subgroup analysis, according to 5-ASA dose, suggested that the use of 3 g or more was associated with a higher frequency of patients that achieved clinical improvement (<2 g [RR 0.79, 95% CI 0.64—0.97] vs. 2–3 g [RR 0.77, 95% CI 0.67—0.88] vs. > 3 g [RR 0.57, 95% CI 0.51—0.65]; p = 0.002).

Oral 5-aminosalicylates vs. sulfasalazine

Nine studies on a total of 909 participants analyzed the comparison. The patients randomly assigned to oral 5-ASA did not experience a higher frequency of remission induction (RR 0.90, 95% CI 0.77–1.04) or endoscopic improvement (RR 0.82, 95% CI 0.65–1.02), nor were differences in the frequency of serious adverse events documented (OR 1.36, 95% CI 0.28–6.52).

In accordance with the type of oral 5-aminosalicylate

Eleven studies including 1,968 participants analyzed the comparison. There was little or no difference in the frequency of clinical remission or adverse events, according to the type of 5-ASA administered (for clinical remission: Asacol RR 0.94, 95% CI 0.85–1.04 vs. Claversal RR 0.95, 95% CI 0.78–1.17 vs. Salofalk RR 0.92, 95% CI 0.72–1.18 vs. Pentasa RR 0.90, 95% CI 0.74–1.10; p = 0.98; and for adverse events: Asacol RR 0.91, 95% CI 0.80–1.03 vs. Claversal RR 1.30, 95% CI 1.01–1.66 vs. Salofalk RR 0.99, 95% CI 0.81–1.20; p = 0.05).

Oral 5-aminosalicylates, according to the number of doses

Five studies that included 1,761 participants compared the effectiveness of administering one daily dose of multimatrix (MMX) mesalazine vs. conventional therapy. There was little or no difference in the frequency of clinical remission (RR 0.99, 95% CI 0.93–1.06) between the groups.

Recommendation No. 3: The use of oral steroids is recommended for inducing remission in patients presenting with UC with moderate-to-severe activity of any extension. Strong, in favor of the strategy. Quality of evidence ⊕⊕⊕◯.

Good practice point: The response to treatment with oral steroids should be evaluated at two to four weeks of treatment. The need to modify treatment should be defined if there is therapeutic failure.

Good practice point: The recommended initial dose of oral prednisolone or prednisone is 40–60 mg/day, and as soon as there is a clinical response (maximum of two weeks), the dose should be gradually reduced until complete suspension, without exceeding a total of 12 weeks of medication use.

Steroids for inducing remission

A systematic review[25] evaluated the safety and effectiveness of steroid use for inducing remission in patients with distal colitis, left-sided colitis, or pancolitis. When com-

pared with placebo, steroid therapy reduced the number of patients that did not achieve clinical remission (RR 0.65, 95% CI 0.45—0.93). Only three trials reported the total number of adverse events associated with the therapy. In general, there was a higher frequency of adverse events in the intervention group (14.3 vs. 7.0% for the control group), albeit the difference was not statistically significant (RR 1.69, 95% CI 0.30–9.62).

Recommendation No. 4: Budesonide MMX is recommended for inducing remission in patients with UC, of any extension, with mild-to-moderate activity. Conditional, in favor of the strategy. Quality of evidence ⊕⊕⊕⊕.

Good practice point: Budesonide MMX can be used in patients that do not respond to 5-ASA medications.

Good practice point: The recommended induction dose of budesonide MMX is 9 mg/day for eight weeks.

Budesonide for inducing remission

A systematic review[26] evaluated the safety and effectiveness of budesonide for inducing remission in patients with proctosigmoiditis, left-sided colitis, or extensive pancolitis.

Budesonide MMX vs. placebo

Three studies with a total of 900 participants analyzed the comparison. The administration of budesonide MMX increased the number of patients that achieved clinical (RR 2.25, 95% CI 1.5–3.39) and endoscopic (RR 1.56, 95% CI 1.13–2.16) remission. Budesonide administration increased the incidence of symptom (RR 1.86, 95% CI 1.25–2.77) and endoscopic (RR 1.29, 95% CI 1.01–1.66) improvement, and was not associated with a higher frequency of serious adverse events (RR 0.63, 95% CI 0.21–1.91).

Acid-resistant budesonide capsules vs. prednisolone

A study with 72 participants carried out the comparison. Treatment with budesonide did not increase the frequency of remission (RR 0.75, 95% CI 0.23–2.42) or endoscopic improvement (RR 0.94, 95% CI 0.66–1.33), nor were there apparent differences in the incidence of histologic remission (RR 0.56, 95% CI 0.15–2.06) or adverse events (RR 0.98, 95% CI 0.4–2.41).

Acid-resistant budesonide capsules vs. mesalamine

Two studies including 600 participants analyzed the comparison. Budesonide therapy was associated with a lower incidence of clinical remission (RR 0.72; 95% CI 0.57—0.91), with little or no difference in the frequency of endoscopic remission (RR 0.78, 95% CI 0.58–1.04).

Recommendation No. 5: The combination of topical and oral aminosalicylates for inducing remission in patients with left-sided or extensive mild-to-moderate UC is recommended. Strong, in favor of the strategy. Quality of evidence ⊕◯◯◯.

Recommendation No. 6: Management with oral mesalazine or sulfasalazine at equivalent doses is recommended for inducing clinical remission in patients with left-sided or extensive UC, with mild-to-moderate activity. Strong, in favor of the strategy. Quality of evidence ⊕⊕⊕◯.

Good practice point: Mesalazine as the first option is preferred to sulfasalazine because of its lower frequency of adverse events.

Good practice point: Treatment response to aminosalicylates should be evaluated at four to eight weeks of treatment. If treatment fails, the need to modify the therapy should be defined.

Good practice point: The dose of oral aminosalicylate for inducing remission should be lower than 2.4 g/day, and the likely ideal dose, equal to or greater than 3 g/day.

Good practice point: One gram of sulfasalazine is equivalent to 400 mg of mesalazine.

Pharmacologic interventions for inducing remission in patients with mild-to-moderate UC

A network meta-analysis[27] (AMSTAR 2: high quality) evaluated the effectiveness of pharmacologic interventions for inducing remission in patients diagnosed with extensive or left-sided mild-to-moderate UC. The review included 48 studies, for a total of 8,020 participants. All the alternatives were superior to placebo, with respect to reducing the frequency of patients that did not achieve remission (mesalazine at a low dose [OR 0.88, 95% CI 0.82—0.94], mesalazine at the standard dose [OR 0.84, 95% CI 0.78—0.91], mesalazine at a high dose [OR 0.75, 95% CI 0.66—0.86], diazo-bonded 5-ASA [OR 0.86, 95% CI 0.76—0.98], sulfasalazine [OR 0.62, 95% CI 0.45—0.87], and budesonide MMX [OR 0.88, 95% CI 0.83—0.94]).

Regarding the direct comparison between interventions, standard or high-dose 5-ASA therapy was associated with a lower incidence of patients that did not achieve clinical remission (OR 0.88, 95% CI 0.79—0.99 and OR 0.81, 95% CI 0.71—0.92, compared with low-dose 5-ASA therapy, respectively), with little or no difference in the standard dose vs. the high dose of 5-ASA (OR 0.94, 95% CI 0.88–1.01). There were also no differences in the comparisons of mesalazine vs. diazo-bonded 5-ASA (OR 1.16, 95% CI 0.94–1.43) and sulfasalazine vs. mesalazine (OR 1.07, 95% CI 0.91–1.26). The combination therapy of oral and rectal 5-ASA was more effective than monotherapy with oral 5-ASA (OR 0.68, 95% CI 0.49—0.94), whereas sulfasalazine was associated with a higher incidence of patients that did not achieve remission (OR 1.30, 95% CI 1.04–1.64), when compared with diazo-bonded 5-ASA.

Evidence from indirect comparisons: failure to induce remission

Combination therapy with oral and rectal 5-ASA was the most effective option, given that it was associated with a lower frequency of patients that did not achieve remission, except when compared with budesonide MMX (OR 0.44,

95% CI 0.23—0.87 vs. diazo-bonded 5-ASA; OR 0.26, 95% CI 0.13—0.51 vs. sulfasalazine; OR 0.39, 95% CI 0.15—0.64 vs. ileal-release budesonide; OR 0.52, 95% CI 0.28—0.97 vs. high doses of mesalazine; OR 0.41, 95% CI 0.22—0.77 vs. standard dose of mesalazine; OR 0.32, 95% CI 0.16—0.61 vs. low dose of mesalazine; and OR 0.49, 95% CI 0.24–1.02 vs. MMX budesonide).

Diazo-bonded 5-ASA therapy was more effective than sulfasalazine (OR 0.57, 95% CI 0.41—0.80) or low-dose mesalazine (OR 0.71, 95% CI 0.51—0.98), whereas sulfasalazine was less effective (OR 1.92, 95% CI 1.16–3.19 vs. budesonide MMX; OR 2.05, 95% CI 1.44–2.92 vs. mesalazine at high doses, and OR 1.61 95% CI 1.16–2.23 vs. mesalazine at standard doses). Mesalazine at high doses was more effective than its standard or low doses (OR 0.78, 95% CI 0.66—0.93 and OR 0.60, 95% CI 0.45—0.80), whereas ileal-release budesonide was associated with a higher frequency of failure to induce remission, when compared with high-dose mesalazine therapy (OR 1.71, 95% CI 1.13–2.57).

Intervention classification from most effective to least effective in inducing remission

Based on the overall results of the network meta-analysis, the 5-ASA combination therapy was the best option when the goal was to induce remission in patients with mild-to-moderate UC (96% probability), followed by mesalazine at high doses (57% probability), budesonide MMX (29% probability), diazo-bonded 5-ASA (40% probability), and the standard dose of mesalazine (55%).

Recommendation No. 7: The use of intravenous cyclosporine is recommended for inducing remission in patients with acute severe UC that is refractory to intravenous steroids. Conditional, in favor of the strategy. Quality of evidence ⊕⊕◯◯.

Good practice point: Cyclosporine or infliximab can be used in patients with acute severe UC that is refractory to intravenous steroids.

Good practice point: Intravenous cyclosporine should be administered at a dose of 2 mg/kg/day.

Good practice point: Intravenous cyclosporine should only be administered at specialized complex care centers by professionals with experience in its use.

Cyclosporine A compared with placebo for inducing remission

A systematic review[28] evaluated the safety and effectiveness of cyclosporine A for inducing remission in patients with acute severe UC. When compared with placebo, cyclosporine A reduced the number of patients that did not achieve clinical remission (OR 0.22, 95% CI 0.07—0.67), with no differences in the incidence of colectomy (OR 0.61, 95% CI 0.18–2.06) or adverse events (OR 3.27, 95% CI 0.44–24.34 for arterial hypertension; OR 7.50, 95% CI 0.46–123.17 for paresthesia).

Cyclosporine A compared with methylprednisolone for inducing remission

A systematic review[28] compared the safety and effectiveness of cyclosporine A and methylprednisolone for inducing remission in patients with refractory severe UC. The administration of cyclosporine A was not associated with a higher frequency of clinical remission (OR 0.71, 95% CI 0.29–1.75), with no differences in the frequency of colectomy (OR 1.00, 95% CI 0.24–4.18), mortality (OR 3.33, 95% CI 0.01–7.58), or adverse events (OR 3.00, 95% CI 0.13–68.26 arterial hypertension).

Recommendation No. 8: The use of oral tacrolimus is not recommended for inducing remission in patients with refractory or steroid-dependent moderate-to-severe UC. Conditional, against the strategy. Quality of evidence ⊕⊕◯◯.

Tacrolimus for inducing remission

A systematic review[29] evaluated the safety and effectiveness of therapy with tacrolimus for the management of patients with refractory or steroid-dependent moderate-to-severe UC. The administration of tacrolimus reduced the number of patients that did not achieve clinical response or mucosal healing (RR 0.58, 95% CI 0.45—0.73 and RR 0.59, 95% CI 0.46—0.74, respectively). Tacrolimus did not increase the incidence of remission induction (RR 0.91 95% CI 0.82–1.00).

Recommendation No. 9: The use of azathioprine as monotherapy is not recommended for inducing remission in patients with UC. Strong, against the strategy. Quality of evidence ⊕◯◯◯.

Azathioprine or 6-mercaptopurines for inducing remission

A systematic review[30] evaluated the effectiveness of azathioprine or 6-mercaptopurines for inducing remission in patients with UC. The administration of azathioprine or 6-mercaptopurines did not increase the number of patients that achieved clinical remission (OR 1.59, 95% CI 0.59–4.29) or symptom improvement (OR 1.44, 95% CI 0.68–3.03).

Recommendation No. 10: The use of methotrexate is not recommended for inducing remission in patients with UC. Strong, against the strategy. Quality of evidence ⊕⊕◯◯.

Methotrexate for inducing remission

A systematic review[31] evaluated the safety and effectiveness of methotrexate for inducing remission in patients with UC. The administration of methotrexate was not associated with a higher frequency of participants that achieved remission (RR 0.96; 95% CI 0.58–1.59).

Recommendation No. 11: The isolated use of an elimination diet is not recommended for inducing remission in patients with UC. Strong, against the strategy. Quality of evidence ⊕◯◯◯.

Good practice point: Along with pharmacologic treatment, patients with UC should receive nutritional guidance.

Good practice point: The effect of a dietary intervention in UC is uncertain. Results from ongoing studies are awaited.

Nutritional intervention (elimination diet) for inducing remission

A systematic review[32] evaluated the effectiveness of nutritional interventions for inducing remission in patients with active UC. When compared with the control groups, patients assigned to the nutritional intervention did not experience a higher frequency of remission induction (RR 8.25, 95% CI 0.50–136.33) or clinical response (RR 4.55, 95% CI 0.63–32.56).

Recommendation No. 12: Fecal microbiota transplant is not recommended for inducing remission in patients with medical treatment-refractory moderate-to-severe UC. Conditional, against the strategy. Quality of evidence ⊕◯◯◯.

Good practice point: Fecal microbiota transplant should be performed in specialized centers with experience in the procedure, as part of a clinical research protocol.

Fecal microbiota transplant for inducing remission

A systematic review[33] evaluated the safety and effectiveness of fecal microbiota transplant for inducing remission in patients with active UC, of any extension, except for proctitis. Fecal microbiota transplant increased the number of patients that achieved remission (RR 1.70, 95% CI 1.12–2.56) or clinical response (RR 1.68, 95% CI 1.04–2.72), with an expected frequency of adverse effects close to 37% (95% CI 22%–56%).

Recommendation No. 13: The use of cannabis is not recommended for inducing remission in patients with mild-to-moderate UC that is refractory to conventional medical treatment. Conditional, against the strategy. Quality of evidence ⊕⊕◯◯.

Cannabis for inducing remission

A systematic review[34] evaluated the safety and effectiveness of therapy based on cannabis for inducing remission in patients with mild-to-moderate UC. The patients assigned to oral cannabinol did not experience a higher frequency of remission (RR 0.94, 95% CI 0.39–2.25), clinical response (RR 1.37, 95% CI 0.59–3.21), or symptom improvement (mean difference [MD] −0.32, 95% CI −0.51 to 1.15 points on the visual analogue scale). A higher number of participants exposed to cannabinol reported adverse effects (RR 1.28, 95% CI 1.05–1.56).

Recommendation No. 14: The use of antibiotics is not recommended for inducing remission in patients with active UC, as adjunct therapy to conventional treatment. Conditional, against the strategy. Quality of evidence ⊕⊕⊕◯.

Good practice point: The panel warns of the risk for bacterial resistance or *Clostridium difficile* infection, with the inadequate use of antibiotics in patients with UC.

Antibiotics for inducing remission

A systematic review[35] evaluated the effectiveness of antibiotic administration for inducing remission in patients with pancolitis, left-sided colitis, or proctitis. Antibiotics reduced the number of patients that did not achieve clinical remission (RR 0.64, 95% CI 0.43—0.96). The subgroup analysis did not suggest any differences, regarding the type of antibiotic (RR 0.68, 95% CI 0.33–1.39 vs. RR 0.46, 95% CI 0.29—0.71 for ciprofloxacin vs. any other antibiotic, $p > 0.05$) or the number of medications administered (RR 0.46, 95% CI 0.29—0.71 vs. RR 0.95, 95% CI 0.84–1.07 for monotherapy vs. numerous antibiotics, $p > 0.05$).

Recommendation No. 15: The use of infliximab is recommended for managing patients with acute severe UC that is refractory to intravenous corticoids. Strong, in favor of the strategy. Quality of evidence ⊕◯◯◯.

Infliximab for inducing remission

A systematic review[36] evaluated the safety and effectiveness of administering infliximab for inducing remission in patients with moderate-to-severe UC. Infliximab increased the frequency of patients that achieved remission (OR 2.8, 95% CI 1.89–4.14) or short-term and long-term clinical response (OR 4.01, 95% CI 3.08–5.23 and OR 3.53, 95% CI 2.55–4.89, for three and 12 months). The participants assigned to receive infliximab had a lower frequency of colectomy (OR 0.38, 95% CI 0.19—0.75 and OR 0.47, 95% CI 0.33—0.67, for three and 12 months), with no higher frequency of adverse events (OR 0.76, 95% CI 0.48–1.19).

Recommendation No. 16: The routine use of an intensified regimen of infliximab is not recommended in patients with acute severe UC. Conditional, against the strategy. Quality of evidence ⊕◯◯◯.

Good practice point: An intensified regimen of infliximab can be considered as acute rescue therapy.

Good practice point: An initial dose of 5 mg/kg of infliximab is preferred to 10 mg/kg, in the multiple dose regimen.

Infliximab for the management of patients with severe UC

A systematic review[37] evaluated the safety and effectiveness of infliximab for the management of patients with acute severe UC. The use of infliximab was classified by dose (5 mg/kg or 10 mg/kg), number of doses (single or multiple dose induction), and frequency of administration, which was catalogued as: (1) standard induction, (2) accelerated induction, and (3) intensified dose induction.

Infliximab 5 mg/kg compared with 10 mg/kg as induction dose

When infliximab administration at a dose of 5 mg/kg was compared with 10 mg/kg as the induction dose, there was

little or no difference in the frequency of colectomy (OR 0.30, 95% CI, 0.08–1.15 at one month; OR 0.37, 95% CI 0.12–1.16 at three months, and OR 0.53, 95% CI 0.19–1.45 at 12 months).

Multiple vs. single induction dose of infliximab 5 mg/kg

When compared with a single induction dose, the multiple dose regimen reduced the number of patients that required colectomy at three months (OR 4.24, 95% CI 2.44–7.36). That benefit was not shown at one month or at 12 months (OR 5.22, 95% CI 0.82–33.14 at one month and OR 1.91, 95% CI 0.79–4.62 at 12 months).

Intensified dose of infliximab compared with the standard dose for induction

When intensified dose therapy for induction was compared with the standard dose, the frequency of colectomy probability was not reduced (OR 0.76, 95% CI 0.34–1.68 at one month; OR 0.70, 95% CI 0.39–1.27 at three months; and OR 0.83, 95% CI 0.55–1.25 at 12 months).

Recommendation No. 17: The use of biologic therapy with tumor necrosis factor-alpha (TNF-α) antagonists (innovator anti-TNF-α drugs or biosimilars) (infliximab, adalimumab, and golimumab), $\alpha 4\beta 7$ integrin inhibitor (vedolizumab), or IL-12/23 inhibitor (ustekinumab) is recommended for inducing remission in patients with moderate-to-severe UC. Strong, in favor of the strategy. Quality of evidence ⊕◯◯◯.

Recommendation No. 18: The use of tofacitinib (JAK inhibitor) is recommended for inducing remission in patients with moderate-to-severe UC. Strong, in favor of the strategy. Quality of evidence ⊕◯◯◯.

Good practice point: Tofacitinib should be used with caution in patients with risk factors for venous thromboembolism, given that an increase in the risk for thrombosis was found in a study on patients with rheumatoid arthritis at a dose of 10 mg every 12 h.

Good practice point: Choosing the first-line medication should depend on patient comorbidities, age, risk factors, cost, and patient preferences.

Good practice point: The biosimilar molecule can be used, according to the local directives of each country. In Latin America, infliximab and adalimumab biosimilars are available.

Recommendation No. 19: Ustekinumab or tofacitinib (JAK inhibitor) use is recommended for inducing clinical remission in patients previously exposed to anti-TNFs that have had no initial response, response loss, or lack of tolerance. Conditional, in favor of the strategy. Quality of evidence ⊕◯◯◯.

Recommendation No. 20: Vedolizumab use is recommended for inducing clinical remission in patients previously exposed to anti-TNFs, when ustekinumab or tofacitinib are not available. Conditional, in favor of the strategy. Quality of evidence ⊕⊕◯◯.

Good practice point: In male patients under 35 years of age, the prolonged use (more than six months) of anti-TNF and thiopurine combination therapy should be limited due to the risk for hepatosplenic T cell lymphoma. Other risk groups for lymphoproliferative disorders should also be verified before using the combination therapy (e.g., negative Epstein-Barr, patients above 65 years of age).

Good practice point: In patients over 65 years of age, the combination therapy should not be used due to a greater risk for lymphoma. In those cases, monotherapy with anti-TNFs is preferable.

Good practice point: In cases of no initial response, response loss, or lack of tolerance to the first biologic, a second biologic with a different mechanism of action is recommended.

Good practice point: Patients with UC treated with tofacitinib should undergo lipid profile monitoring and have a prior vaccination against herpes zoster, whenever it is available and possible.

Good practice point: Induction treatment with tofacitinib at a dose of 10 mg every 12 h should not be given for more than 16 weeks, in the case of no response. The maintenance dose is 5 mg twice a day.

Good practice point: If a non-medical switch from an innovator biologic to a biosimilar is carried out, the treating physician should be previously informed for his/her opinion and drug surveillance. The patient should also consent to the change in therapy.

Infliximab compared with cyclosporine in managing patients with severe UC

A systematic review[38] compared the safety and effectiveness of infliximab with cyclosporine for the management of patients with steroid-refractory acute severe UC.

Evidence from controlled clinical trials

Three controlled clinical trials, with a total of 412 participants, analyzed the comparison. Infliximab therapy did not increase the probability of therapeutic response (OR 1.08, 95% CI 0.73–1.60), with similar colectomy rates at follow-up at three (OR 1.00, 95% CI 0.64–1.59) or 12 (OR 0.76; 95% CI 0.51–1.14) months. There were no differences in the frequency of serious adverse events (OR 1.41, 95% CI 0.08–2.09).

Evidence from observational studies

Ten cohort studies that included 854 patients provided data on the comparison. When compared with cyclosporine, infliximab therapy was associated with a higher probability of therapeutic response (OR 2.96, 95% CI 2.12–4.14), together with a lower frequency of colectomy at 12 months (OR 0.42, 95% CI 0.22—0.83). There were no differences in

the frequency of serious adverse events (OR 0.69, 95% CI 0.35–1.33), postoperative complications (OR 1.05, 95% CI 0.40–2.77), or mortality (OR 1.37, 95% CI 0.31–6.10).

Good practice point: Infliximab or cyclosporine can be used in patients with acute severe UC that is refractory to intravenous steroids.

Adalimumab for inducing remission

A systematic review[39] evaluated the safety and effectiveness of adalimumab for inducing remission in patients diagnosed with steroid-refractory, moderate-to-severe UC. Therapy based on adalimumab increased the number of patients that achieved remission (RR 1.50, 95% CI 1.08–2.09) or clinical response (RR 1.33; 95% CI 1.16–1.52). Adalimumab administration was also associated with a higher incidence of mucosal healing (RR 1.21, 95% CI 1.04–1.41) and higher scores on the inflammatory bowel disease questionnaire (IBDQ) (RR 1.23, 95% CI1.06—1.43).

Vedolizumab for inducing remission

A systematic review[40] evaluated the safety and effectiveness of vedolizumab for inducing remission in patients with moderate-to-severe UC. Vedolizumab administration reduced the number of patients that did not achieve clinical (RR 0.86, 95% CI 0.80—0.91) or endoscopic (RR 0.82, 95% CI 0.75—0.91) remission, which was not reflected in a higher frequency of serious adverse events (RR 0.99, 95% CI 0.93–1.07).

Safety and effectiveness of biosimilars

A systematic review[41] evaluated the safety and effectiveness of biosimilars for treating patients with moderate-to-severe UC. The studies included in the review recruited patients with no previous exposure to biologics or that rotated from infliximab therapy to biosimilar therapy. The exposure to the biosimilar was associated with a 66% weighted percentage for clinical response (95% CI 63–72%), which varied from 68% (95% CI 63–72%) at week eight to 54% (95% CI 45–63%) at week 48 of follow-up. On the other hand, exposure to the biosimilar resulted in a 49% weighted percentage for clinical remission (95% CI 44–53%) that again varied from 48% (95% CI 43–56%) at week eight to 47% (95% CI 36–59%) at week 48.

Regarding the sustained clinical response, exposure to the biosimilar was associated with a 91% weighted response (95% CI 59–98%), which varied from 95% (95% CI 57–99%) at week 32–83% (95% CI 19–99%) at week 48 of follow-up. On the other hand, exposure to the biosimilar resulted in a 74% weighted percentage for sustained clinical remission (95% CI 62–84%) that again varied from 62% (95% CI 49–73%) at week 16–77% (95% CI 70–82%) at week 48. Lastly, the weighted frequency of adverse effects associated with the therapy was 9% (95% CI 4–18%), in patients exposed to the biosimilar that had no previous exposure to a biologic.

Second anti-TNF biologic in patients with UC that had failure with a first anti-TNF medication

A systematic review[42] evaluated the safety and effectiveness of using a second biologic for inducing remission in patients with UC that experienced failure with a first biologic medication. The systematic review did not include a meta-analysis. The studies retrieved corresponded to case series that reported the number of patients achieving remission (nine studies and 356 patients). Exposure to a second biologic produced apparent clinical remission in 16% (range: 0–16%) of the cases with primary failure (non-response). Regarding secondary failure (loss of response), the number of exposed patients that achieved remission ranged from 10 to 27%; when the first biologic was removed due to intolerance, the figure was 25–50%. With respect to clinical response, exposure to a second biologic produced an apparent response in 23–92% of the cases with primary failure (non-response). Regarding secondary failure (loss of response) the number of exposed patients that achieved response ranged from 38 to 85%; when the first biologic was removed due to intolerance, the figure was 61% (datum provided by a single case series with that result in eight out of 13 patients). In the patients with UC, the number of adverse events associated with the therapy ranged from 20 to 39%, with a frequency of serious adverse events close to 7%. The abandonment of secondary therapy due to adverse events was reported in 0–48% of the participants.

Biologics for inducing remission in patients with moderate-to-severe UC

A network meta-analysis[43] evaluated the effectiveness of biologic medications for inducing remission in patients above 18 years of age with moderate-to-severe UC. The studies included were characterized by recruiting participants with active UC, with or without previous exposure to anti-TNFs.

First-line therapy

Fifteen studies included 3,747 participants with moderate-to-severe UC, with no previous exposure to anti-TNFs. All the alternatives were more effective than placebo for inducing clinical remission (infliximab OR 4.07, 95% CI 2.68–6.16; adalimumab OR 1.8, 95% CI 1.17–2.77; golimumab OR 2.80, 95% CI 1.68–4.67; tofacitinib OR 2.12, 95% CI 1.13–3.98; ustekinumab OR 2.04, 95% CI 1.04–4.02; and vedolizumab OR 3.10, 95% CI 1.53–6.26). One study compared vedolizumab with adalimumab and found no apparent differences between groups for that outcome (OR 1.24, 95% CI 0.86–1.78).

Regarding the active interventions (network meta-analysis), when compared with infliximab, the administration of adalimumab (OR 0.48, 95% CI 0.26—0.86) and golimumab (OR 0.52, 95% CI 0.33—0.83) was associated with a lower incidence of remission induction. No other significant differences between interventions were found. Based on the overall conclusions of the network meta-analysis, infliximab was the best option when the goal was to induce clinical remission in patients with no previous exposure to

anti-TNFs (95% probability), followed by golimumab (68% probability), vedolizumab (63% probability), tofacitinib (47% probability), ustekinumab (42% probability), and lastly, adalimumab (35% probability).

Second-line therapy

Seven studies included 1,580 participants with moderate-to-severe UC and previous exposure to anti-TNFs. They started second-line treatment due to loss of response, inadequate response, or inability to tolerate the medication. Tofacitinib (OR 11.88, 95% CI 2.32–60.89) and ustekinumab (OR 11.51, 95% CI 2.65–49.96) were superior to placebo, with little or no difference from adalimumab (OR 1.36, 95% CI 0.49–3.80) or vedolizumab (OR 1.55, 95% CI 0.58–4.16). One study compared vedolizumab with adalimumab and found no apparent differences (OR 2.10, 95% CI 0.90–4.88).

In the active intervention comparison (network meta-analysis), indirect evidence suggested that ustekinumab, when compared with vedolizumab or adalimumab, was associated with a higher incidence of remission induction (OR 5.99, 95% CI 1.13–31.76 and OR 10.71, 95% CI 2.01–57.20, respectively). The administration of tofacitinib was also associated with a higher incidence of remission induction, when compared with vedolizumab or adalimumab (OR 6.18, 95% CI 1.00–38.00 and OR 11.05, 95% CI 1.79–68.41, respectively). No significant differences were found in the comparison of ustekinumab vs. tofacitinib (OR 0.97, 95% CI 0.11–8.72).

Thus, based on the overall conclusions of the network meta-analysis, both ustekinumab and tofacitinib were the best alternatives when the goal was to induce clinical remission in patients previously exposed to anti-TNFs (87% probability for the two options), followed by vedolizumab (48% probability), and lastly, adalimumab (15% probability).

Question: What is the safety and effectiveness of the pharmacologic and non-pharmacologic interventions that enable remission to be maintained in patients with UC?

Recommendation No. 21: Management with topical rectal aminosalicylate is recommended for maintaining clinical remission in patients with ulcerative proctitis. Conditional, in favor of the strategy. Quality of evidence ⊕⊕◯◯.

Good practice point: Doses of 500 or 1,000 mg of topical aminosalicylate for maintaining remission does not appear to affect efficacy, and suppositories are the more convenient presentation, compared with enemas.

Recommendation No. 22: Management with oral aminosalicylates is recommended for maintaining clinical and endoscopic remission in patients with mild-to-moderate UC. Strong, in favor of the strategy. Quality of evidence ⊕⊕⊕◯.

Recommendation No. 23: The use of oral mesalazine or sulfasalazine is recommended for maintaining remission in patients with mild-to-moderate UC. Strong, in favor of the strategy. Quality of evidence ⊕⊕◯◯.

Good practice point: No differences were found in the use of equivalent doses of conventional or prolonged-release oral mesalazine, for maintaining remission in patients with mild-to-moderate UC.

Good practice point: The maintenance dose of 5-ASA in patients with mild-to-moderate UC should be based on clinical, biomarker (ideally fecal calprotectin) or endoscopic criteria.

Good practice point: The minimum aminosalicylate dose for maintaining clinical remission in mild-to-moderate UC is 1.5 g/day.

Recommendation No. 24: The use of thiopurines is recommended for maintaining remission in patients with corticosteroid-dependent or corticosteroid-resistant UC. Conditional, in favor of the strategy. Quality of evidence ⊕⊕◯◯.

Good practice point: The recommended dose of azathioprine is 2.0–2.5 mg/kg/day.

Good practice point: The recommended dose of 6-mercaptopurine is 1.0–1.5 mg/kg/day.

Good practice point: Steroid dependence or excess is considered in patients that present with relapse with a dose <15 mg of prednisolone, or relapse within the three months after its suspension, or that receive two or more courses of steroids in one year.

Good practice point: Before using immunosuppressants, the presence of infectious diseases must be ruled out.

Good practice point: Patients being treated with thiopurines should be monitored for hematologic and hepatic toxicity.

Rectal 5-aminosalicylates for maintaining remission

A systematic review[23] analyzed the safety and effectiveness of rectal 5-aminosalicylates, for maintaining remission in patients with UC in clinical and endoscopic remission.

Rectal 5-aminosalicylates vs. placebo

Four studies with 301 participants analyzed the comparison. The patients assigned to receive rectal 5-aminosalicylates continued to have a higher frequency of a period with clinical (RR 2.22, 95% CI 1.26–3.90) or endoscopic (RR 4.88; 95% CI 1.31–18.18) remission. No differences in the frequency of adverse events were documented (RR 1.35, 95% CI 0.63–2.89).

Rectal 5-aminosalicylates vs. oral 5-aminosalicylates

Two studies with 91 participants compared the two interventions. The patients assigned to receive rectal 5-aminosalicylates did not have a higher frequency of clinical (RR 1.24, 95% CI 0.92–1.66) or endoscopic (RR 1.14, 95% CI 0.90–1.45) relapse. No differences were found in the frequency of adverse events (RR 0.21, 95% CI 0.01–4.26).

Oral 5-aminosalicylates for maintaining remission

A systematic review[44] evaluated the safety and effectiveness for maintaining remission in patients with mild-to-moderate UC in remission.

Oral 5-aminosalicylates vs. placebo

Nine studies with 1,555 participants analyzed the comparison. The patients assigned to receive oral 5-aminosalicylate had a lower frequency of relapse (RR 0.68, 95% CI 0.61—0.71), with no difference in the frequency of serious adverse events (RR 0.60, 95% CI 0.19–1.84).

Oral 5-aminosalicylates vs. sulfasalazine

Twelve studies with 1,655 participants compared the therapies. The patients assigned to receive oral 5-aminosalicylates had a higher frequency of relapse (RR 1.14, 95% CI 1.03–1.27), with no differences in the incidence of adverse events (RR 1.07, 95% CI 0.82–1.40).

In accordance with the type of oral 5-aminosalicylate (prolonged-release mesalazine vs. traditional mesalazine)

Six studies with 707 participants compared the two therapies. The use of prolonged-release mesalazine did not reduce the frequency of clinical or endoscopic relapse (RR 1.08, 95% CI 0.91–1.28) and was not associated with a lower frequency of serious adverse events (RR 0.56, 95% CI 0.14–2.22).

In accordance with the dose of oral 5-aminosalicylate (>2 g/day vs. <2 g/day)

Ten studies with 1,781 participants analyzed the comparison. Therapy at high doses of 5-aminosalicylates was not associated with a lower frequency of clinical or endoscopic relapse (RR 0.85, 95% CI 0.78–1.00) or with a higher incidence of serious adverse events (RR 1.11, 95% CI 0.43–2.82).

Azathioprine or 6-mercaptopurine for maintaining remission

A systematic review[45] evaluated the safety and effectiveness of the use of azathioprine or 6-mercaptopurine for maintaining remission in patients with active UC that was resistant or non-resistant to steroids.

Azathioprine vs. placebo

Four studies with 232 participants analyzed the comparison. The patients assigned to receive azathioprine had a lower frequency of relapse (RR 0.68, 95% CI 0.54—0.86) that was not accompanied by a greater frequency of adverse events (RR 2.51, 95% CI 0.82–7.14).

Azathioprine vs. sulfasalazine or cyclosporine

Two studies with 41 participants compared the interventions. The patients assigned to receive azathioprine did not have a higher or lower frequency of relapse (RR 1.52, 95% CI 0.66–3.50). When compared with the use of cyclosporine, azathioprine did not reduce the frequency of relapse (RR 0.80, 95% CI 0.33–1.92) or adverse events (RR 0.20, 95% CI 0.03–1.35).

6-mercaptopurine vs. 5-aminosalicylates or methotrexate

Two studies with 51 participants analyzed the comparisons. The patients assigned to receive 6-mercaptupurine, when compared with the 5-aminosilacylates, had a lower frequency of relapses (RR 0.53, 95% CI 0.31—0.90), with no apparent differences in the frequency of adverse events (RR 4.20; 95% CI 0.24–72.29). The administration of 6-mercaptupurine was associated with a lower number of patients that did not continue in remission, when compared with methotrexate (RR 0.55; 95% CI 0.31—0.95), and the profile regarding side effects (RR 1.29, 95% CI 0.26–6.46) was similar.

Pharmacologic interventions for maintaining remission in patients with mild-to-moderate UC

A network meta-analysis[27] evaluated the effectiveness of different pharmacologic interventions for maintaining remission in patients diagnosed with mild-to-moderate UC, with extensive or left-side involvement.

Evidence from direct comparisons: remission maintenance failure

The review included 48 studies, for a total of 8,020 participants. Therapy with sulfasalazine (OR 0.45, 95% CI 0.23—0.89) or 5-ASA was likely to be more effective than placebo (OR 0.63, 95% CI 0.51—0.79, for the comparison with low-dose 5-ASA vs. placebo; and OR 0.55, 95% CI 0.43—0.70, for the comparison of standard dose 5-ASA vs. placebo), with little or no difference, with respect to the use of diazo-bonded 5-ASA (OR 0.71, 95% CI 0.41–1.21).

When compared with low doses, standard 5-ASA therapy was likely to be associated with a lower incidence of patients that did not achieve remission maintenance (OR 0.85, 95% CI 0.72—0.99), with little or no difference when comparing standard dose vs. high-dose 5-ASA (OR 0.93, 95% CI 0.73–1.17). When compared with the use of diazo-bonded 5-ASA, mesalazine was likely to be associated with a higher number of patients that did not achieve remission maintenance (OR 1.45, 95% CI 1.06–1.98), with little or no difference in relation to the comparisons of sulfasalazine vs. diazo-bonded 5-ASA (OR 1.07, 95% CI 0.98–1.16) or sulfasalazine vs. mesalazine (OR 1.13, 95% CI 0.91–1.40). Lastly, the combination therapy of oral and rectal 5-ASA was likely to be more effective than monotherapy with oral 5-ASA (OR 0.45, 95% CI 0.20—0.97).

Evidence from indirect comparisons: remission maintenance failure

All the interventions were more effective than placebo (OR 3.85, 95% CI 1.56–9.49 for oral and rectal 5-ASA; OR 2.17, 95% CI 1.46–3.21 for diazo-bonded 5-ASA; OR 2.72, 95% CI 1.91–3.86 for sulfasalazine; OR 3.50, 95% CI 2.19–5.57 for

high doses of mesalazine; OR 3.02, 95% CI 2.28–4.01 for standard dose of mesalazine; OR 2.18, 95% CI 1.62–2.84 for low dose of mesalazine) and high doses or the standard dose of mesalazine was superior to low doses (OR 0.62, 95% CI 0.40—0.97 and OR 0.72, 95% CI 0.57—0.92).

Intervention classification from the most effective to the least effective: remission maintenance

Based on the overall results of the network meta-analysis, the combination therapy with 5-ASA was the best option when the goal was to maintain remission in patients with mild-to-moderate UC (57% probability), followed by mesalazine at high doses (42% probability), mesalazine at the standard dose (45% probability), sulfasalazine (49% probability), mesalazine at low doses (49% probability), and diazo-bonded 5-ASA (49% probability).

Recommendation No. 25: The use of probiotics is not recommended for maintaining remission in patients with UC. Strong, against the strategy. Quality of evidence ⊕◯◯◯.

Recommendation No. 26: The concomitant administration of probiotics with aminosalicylates is not recommended for maintaining remission in patients with UC. Strong, against the strategy. Quality of evidence ⊕◯◯◯.

Probiotics for maintaining remission

A systematic review[46] evaluated the safety and effectiveness of the use of probiotics for maintaining remission in patients with inactive UC.

Probiotics vs. placebo

Four studies with 361 participants analyzed the comparison. The patients assigned to receive probiotics did not have a lower frequency of medium-term (RR 0.87, 95% CI 0.63–1.18) or long-term (RR 1.16; 95% CI 0.98–1.37) relapse. Probiotic administration apparently did not increase quality-of-life scores (difference in means [DM] —0.7 points; 95% CI —1.63 to 0.23).

Probiotics plus 5-aminosalicylates vs. 5-aminosalicylates

Two studies with 242 participants analyzed the comparison. When compared with monotherapy, the concomitant administration of probiotics plus 5- aminosalicylates was not associated with a lower frequency of medium-term (RR 1.05, 95% CI 0.89–1.24) or long-term (RR 1.11, 95% CI 0.66–1.87) relapse.

Recommendation No. 27: The use of nutritional therapy is not recommended for maintaining remission in patients with UC. Conditional, against the strategy. Quality of evidence ⊕◯◯◯.

Good practice point: Nutritional guidance that accompanies pharmacologic treatment should be given to patients with UC.

Nutritional intervention for maintaining remission

A systematic review[32] evaluated the effectiveness of nutritional interventions for maintaining remission in patients with UC in clinical remission. The patients assigned to nutritional intervention did not have a lower frequency of relapse (RR 1.25, 95% CI 0.42–3.70 for the Alberta diet; RR 0.50, 95% CI 0.15–1.64 for the carrageenin-free diet; and RR 0.83, 95% CI 0.60–1.15 for the gluten-free or dairy-free diet). Nutritional interventions had little or no effect on quality-of-life scores in patients with UC (difference in means [DM] 1.7, 95% CI —4.83 to 8.23 points on the SIBDQ scale).

Recommendation No. 28: The use of turmeric as monotherapy is not recommended for maintaining remission in patients with UC. Conditional, against the strategy. Quality of evidence ⊕◯◯◯.

Turmeric for maintaining remission

A systematic review[47] evaluated the effectiveness of turmeric for maintaining remission in patients with UC. The patients assigned to receive turmeric did not have a lower frequency of medium-term or short-term relapse (RR 0.24, 95% CI 0.05–1.09 at follow-up at six months and RR 0.70, 95% CI 0.35–1.40 at follow-up at 12 months), but they did have a higher score on the clinical (difference in means [DM] —1.2, 95% CI —0.26 to 2.14 points on the CAI) and endoscopic (difference in means [DM] —0.8, 95% CI —0.27 to 1.33 points on the de Rachmilewitz scale) activity indexes at follow-up at six months.

Recommendation No. 29: The use of biologic therapy with tumor necrosis factor-alpha antagonists (innovator anti-TNF-α drugs or biosimilars) (infliximab, adalimumab, and golimumab), $\alpha 4\beta 7$ integrin inhibitor (vedolizumab), and IL-12/23 inhibitor (ustekinumab) is recommended for maintaining remission in patients with moderate-to-severe UC. Strong, in favor of the strategy. Quality of evidence ⊕⊕◯◯.

Recommendation No. 30: The use of tofacitinib (JAK inhibitor) is recommended for maintaining remission in patients with moderate-to-severe UC. Strong, in favor of the strategy. Quality of evidence ⊕⊕◯◯.

Good practice point: Tofacitinib should be used with caution in patients with risk factors for venous thromboembolism because an increase in the risk for thrombosis was found at a dose of 10 mg every 12 h, in a study on patients with rheumatoid arthritis.

Good practice point: To maintain remission, the same drug with which remission was induced should be continued.

Good practice point: When there is apparent loss of response during maintenance, causes that are not inherent to the effectiveness of the drug should be ruled out, such as poor treatment adherence, cytomegalovirus infection, and *Clostridium difficile* or some other enteropathogen.

Good practice point: When there is loss of effectiveness of the drug for maintaining remission, treatment should be optimized or eventually changed to another drug, taking into account the determination, when available, of serum monoclonal antibody levels and the presence of antibodies.

Good practice point: Patients above 65 years of age being treated with anti-TNF drugs are at greater risk for infections.

Adalimumab for maintaining remission

A systematic review[39] evaluated the safety and effectiveness of the administration of adalimumab for inducing remission in patients diagnosed with moderate-to-severe UC that is refractory to steroids. Therapy based on adalimumab increased the number of patients that remained in clinical remission at follow-up at 52 weeks (RR 2.38, 95% CI 1.57–3.59) or that continued to have clinical response (RR 1.69, 95% CI 1.29–2.21). Adalimumab was also associated with a higher incidence of mucosal healing (RR 1.69, 95% CI 1.26–2.28), with higher scores on the IBDQ (RR 1.73, 95% CI 1.28–2.34), and with patients in steroid-free remission (RR 2.22; 95% CI 1.10–4.17). Therapy with adalimumab did not increase the frequency of serious adverse events (RR 1.09, 95% CI 0.78–1.53), but did increase the incidence of reactions at the administration site (RR 2.52, 95% CI 1.48–4.28).

Vedolizumab for maintaining remission

A systematic review[40] evaluated the safety and effectiveness of vedolizumab for maintaining remission in patients with moderate-to-severe UC. The administration of vedolizumab reduced the number of patients that had clinical (RR 0.67, 95% CI 0.59—0.77) or endoscopic (RR 0.58, 95% CI 0.49—0.68) relapse, with no higher frequency of very serious adverse events (RR 1.02, 95% CI 0.73–1.42).

Tofacitinib (JAK inhibitor) for maintaining remission

A systematic review[48] evaluated the safety and effectiveness of tofacitinib for maintaining remission in patients with moderate-to-severe UC. The patients assigned to receive tofacitinib had a lower frequency of clinical (RR 0.70, 95% CI 0.64—0.77) and endoscopic (RR 0.88, 95% CI 0.83—0.92) relapse, that was not accompanied by a higher frequency of serious adverse events (RR 0.81, 95% CI 0.42–1.59).

Biologics for maintaining remission in moderate-to-severe UC

A network meta-analysis[43] evaluated the effectiveness of biologic medications for maintaining remission in patients above 18 years of age, with moderate-to-severe UC.

Studies that continued the intervention assigned as maintenance therapy (first-line)

A total of seven studies included 1,844 participants with moderate-to-severe UC that were not previously exposed to anti-TNF drugs. Infliximab and adalimumab were both more effective than placebo (OR 2.89, 95% CI 1.96–4.25 and OR 2.51, 95% CI 1.52–4.15, respectively). One study compared vedolizumab with adalimumab and reported that the incidence of remission maintenance was higher in the patients treated with vedolizumab (OR 1.62, 95% CI 1.14–2.31). Based on the overall conclusions of the network meta-analysis, indirect evidence suggested that vedolizumab was the best option when the goal was to maintain clinical remission in patients that were not previously exposed to anti-TNF drugs (93% probability), followed by infliximab (63% probability), and adalimumab (44% probability).

Studies that again randomized patients that responded to induction therapy (second-line)

All the options were superior to placebo (golimumab OR 2.70, 95% CI 1.60–4.58; tofacitinib OR 4.18, 95% CI 2.46–7.12; ustekinumab OR 2.46, 95% CI 1.56–3.89; and vedolizumab OR 3.80, 95% CI 2.31–6.23). Based on the overall conclusion of the network meta-analysis, golimumab or tofacitinib was the best option, when the goal was to maintain clinical remission in patients previously exposed to anti-TNF drugs (69% probability), followed by vedolizumab (63% probability) and ustekinumab (47% probability).

Question: What is the safety and effectiveness of the pharmacologic and non-pharmacologic interventions for managing pouchitis in patients with UC?

Recommendation No. 31: The use of ciprofloxacin as the first option is recommended for inducing remission in patients with acute pouchitis. Conditional, in favor of the strategy. Quality of evidence ⊕◯◯◯.

Good practice point: The dose of ciprofloxacin is 500 mg orally every 12 h, for two to four weeks.

Recommendation No. 32: The use of metronidazole is recommended for inducing remission in patients with acute pouchitis, when it is not possible to administer ciprofloxacin. Conditional, in favor of the strategy. Quality of evidence ⊕◯◯◯.

Ciprofloxacin compared with metronidazole for inducing remission in patients with pouchitis

A systematic review[28] compared the safety and effectiveness of the use of ciprofloxacin with metronidazole, for inducing remission in patients with pouchitis. Compared with metronidazole, the administration of ciprofloxacin increased the incidence of clinical remission (RR 2.68, 95% CI 1.13–6.35), with no apparent difference in the frequency of adverse events (RR 0.18, 95% CI 0.01–2.98).

Recommendation No. 33: The use of innovator anti-TNF or biosimilar therapy (infliximab or adalimumab) is recommended for inducing and maintaining remission in patients with chronic pouchitis that is refractory to conventional treatment. Conditional, in favor of the strategy. Quality of evidence ⊕◯◯◯.

Recommendation No. 34: The use of vedolizumab is recommended for inducing and maintaining remission in patients with chronic pouchitis that is refractory to conventional treatment (infliximab or adalimumab). Conditional, in favor of the strategy. Quality of evidence ⊕◯◯◯.

Biologic therapy for managing patients with pouchitis

Therapy with anti-TNF drugs for inducing and maintaining remission in patients with chronic refractory pouchitis.

A systematic review[49] (AMSTAR 2: critically low confidence) evaluated the effectiveness of anti-TNF therapy for inducing and maintaining remission in patients with chronic refractory pouchitis. The majority of the studies

were case series that reported the number of patients with chronic refractory pouchitis that achieved remission induction or maintenance (seven studies, 133 patients). The patients exposed to anti-TNF therapy had a frequency of remission induction close to 17% (95% CI 1–40%), with a frequency of remission maintenance of 37% (95% CI 14–62%).

Adalimumab compared with placebo for managing patients with chronic refractory pouchitis

A multicenter, masked, placebo-controlled randomized clinical trial,[50] evaluated the safety and effectiveness of adalimumab for managing chronic refractory pouchitis. Adalimumab therapy was associated with better clinical disease activity index scores (RR 3.50, 95% CI 1.08–11.29) that was not apparently reflected in a higher remission rate (RR 1.17, 95% CI 0.09–14.92) or clinical response rate (RR 1.17, 95% CI 0.36–3.76). The administration of adalimumab did not increase the frequency of participants with endoscopic improvement (RR 4.67; 95% CI 0.70–31.22) or better quality of life (RR 1.13, 95% CI 0.20–6.24).

Vedolizumab for managing patients with chronic refractory pouchitis

A systematic review[51] compiled available evidence on the use of vedolizumab in patients with chronic refractory or antibiotic-dependent pouchitis. The literature search produced seven studies (case series or case reports) on the use of vedolizumab in patients with chronic refractory pouchitis. The first case report was on a patient that developed pouchitis 14 years after undergoing ileoanal anastomosis, that was refractory to metronidazole, VSL #3, budesonide, mesalamine, rectal hydrocortisone, and fecal microbiota transplant. He was started on vedolizumab, with apparent clinical and endoscopic response at month six. The second case was a man that developed antibiotic and anti-TNF-refractory pouchitis three months after undergoing ileoanal anastomosis. He was started on vedolizumab and had apparent clinical response at follow-up week 34. The third case was a female patient who developed pouchitis two years after undergoing anastomosis. She was managed with trimethoprim-sulfamethoxazole and rifaximin, obtaining partial response. When started on vedolizumab, she showed apparent clinical response at week six. At month six of treatment, endoscopy revealed the presence of a linear ulcer and healthy mucosa in the ileal pouch.

Another case report was on a woman who developed chronic pouchitis one year after undergoing ileoanal anastomosis. She was managed with antibiotics and oral budesonide, obtaining partial response. She was then started on adalimumab, without achieving remission, and was switched to vedolizumab. The patient reported clinical response at week 12 and at month six of treatment. Another case report described a woman with pouchitis diagnosed one year after undergoing anastomosis, and initially treated with antibiotics and prednisolone. Due to refractoriness, she was started on infliximab, followed by adalimumab, but both interventions were suspended because of severe allergic reactions and loss of response. She received vedolizumab, together with a single course of antibiotics, achieving apparent clinical response. Endoscopy documented no apparent active disease after 33 weeks of treatment.

The first case series on exposure to vedolizumab in patients with chronic pouchitis documented its use in 20 participants, 12 of whom were women, with a mean age of 22 years. Eleven of the patients had received previous management with anti-TNF drugs, without achieving response. All the patients were treated with vedolizumab, with apparent clinical response in 13 of them, after 14 weeks of treatment. The endoscopic evaluation reported response in nine of the patients at week 14. The activity index of the ileal pouch, utilized to establish endoscopic improvement, decreased from 10 to 3. Lastly, Singh et al. reported their experience with a case series, describing the result of exposure in 19 patients, nine of whom were previously treated with anti-TNF drugs. Fifteen participants reported clinical response to vedolizumab, 14 had clinical and endoscopic response, and four had treatment failure.

Question: What is the safety and effectiveness of the different interventions for managing patients with UC that require surgical treatment?

Manual ileoanal anastomosis compared with stapled ileoanal anastomosis

Recommendation No. 35: The surgical management of patients with UC should be performed at specialized complex care institutions with experience in the management of those types of patients (at least 10 procedures per year). Strong, in favor of the strategy. Quality of evidence ⊕◯◯◯.

Good practice point: The choice of the technique for the ileoanal anastomosis should be individualized according to patient characteristics (presence of distal rectal dysplasia), equipment availability, and surgical experience. Strong, in favor of the strategy. Quality of evidence ⊕◯◯◯.

Good practice point: Mucosectomy should be utilized in patients with high-grade rectal dysplasia. Strong, in favor of the strategy. Quality of evidence ⊕◯◯◯.

A systematic review[52] analyzed the use of manual ileoanal anastomosis, compared with the stapled procedure in adults with UC. When compared with the stapled ileoanal anastomosis, the manual procedure was associated with a higher frequency of watery stool incontinence (OR 2.32, 95% CI 1.24–4.34) and episodes of nocturnal incontinence (OR 2.78, 95% CI 1.70–4.56). There were no differences in the incidence of anastomotic leaks (OR 1.18, 95% CI 0.79–1.78), pelvic sepsis (OR 1.50, 95% CI 0.80–2.82), fistulas related to the ileal pouch (OR 1.35, 95% CI 0.75–2.42), anastomotic stricture (OR 1.47, 95% CI 0.81–2.66), ileal pouch failure (OR 1.73, 95% CI 0.99–3.04), or the development of pouchitis (OR 1.08, 95% CI 0.60–1.94).

Laparoscopic ileal pouch and ileoanal anastomosis compared with laparotomy-assisted ileal pouch and ileoanal anastomosis

Recommendation No. 36: The minimally invasive (laparoscopic) approach is recommended when performing the reconstructive proctocolectomy with ileal pouch and the

ileoanal anastomosis in patients with UC. Strong, in favor of the strategy. Quality of evidence ⊕⊕◯◯.

A systematic review[53] compared the use of laparoscopic-assisted ileoanal anastomosis with laparotomy-assisted ileoanal anastomosis. The former was associated with shorter hospital stay (DM −2.66 days, 95% CI −1.04–4.28 days) and a shorter time interval for starting oral diet (DM −1.48 days; 95% CI −0.25—2.71 days), but longer surgery duration (DM 91.52 min, 95% CI 53.36–129.68 min). No differences in the incidence of complications (RR 0.81, 95% CI 0.32–2.02), severe postoperative complications (RR 0.65, 95% CI 0.29–1.48), or non-severe postoperative complications (RR 1.05, 95% CI 0.78–1.41) were documented.

Different ileal pouch techniques

Recommendation No. 37: The J-pouch technique is recommended when performing reconstructive proctocolectomy with ileoanal anastomosis, in patients with UC. Conditional, in favor of the strategy. Quality of evidence ⊕◯◯◯.

Good practice point: In patients with failed reconstructive proctocolectomy, new reconstruction with a J-pouch should be considered, whenever feasible. Conditional, in favor of the strategy. Quality of evidence ⊕◯◯◯.

Good practice point: The K-pouch (Kock pouch) can be an option for managing patients that are not candidates for reconstructive proctocolectomy with J-pouch ileoanal anastomosis (sphincteric lesion) or for patients in whom ileostomy would be a considerable problem (leaks, skin problems). Conditional, in favor of the strategy. Quality of evidence ⊕◯◯◯.

Recommendation No. 38: Annual endoscopy of the ileal pouch should be carried out in patients with UC and risk factors for neoplasia. Conditional, in favor of the strategy. Quality of evidence ⊕◯◯◯.

A systematic review[54] (AMSTAR2: critically low confidence) compared the different techniques for constructing the ileal pouch in patients with UC.

J-pouch vs. W-pouch

Four randomized trials with 211 participants analyzed the comparison. The frequency of dehiscence and stricture of the anastomosis was similar between the groups (OR 3.20, 95% CI 0.31–32.66 and OR 0.40, 95% CI 0.06–2.62), as was the incidence of wound infection (OR 0.57, 95% CI 0.16–2.00), pelvic sepsis (OR 1.72, 95% CI 0.67–4.46), ileal pouch fistula (OR 0.62, 95% CI 0.09–4.02), and intestinal obstruction (OR 1.04, 95% CI 0.38–2.84).

K-pouch vs. J-pouch

A randomized trial with 55 participants made the comparison. There were no significant differences in relation to dehiscence or stricture of the anastomosis (OR 1.76, 95% CI 0.27–11.47 and OR 1.12, 95% CI 0.07–18.86), intestinal obstruction (OR 0.35, 95% CI 0.03–3.56), or bleeding or inflammation of the ileal pouch (OR 0.36, 95% CI 0.01–9.19 and OR 2.60, 95% CI 0.58–11.69).

S-pouch vs. J-pouch

Six observational studies with control groups and 917 participants analyzed the comparison. No differences were found, with respect to dehiscence or stricture of the anastomosis (OR 0.76, 95% CI 0.22–2.58 and OR 2.15, 95% CI 0.68–6.81), wound infection or pelvic sepsis (OR 1.07, 95% CI 0.42–2.70 and OR 0.89, 95% CI 0.27–2.93, respectively), ileal pouch fistula (OR 0.66, 95% CI 0.38–1.13), or intestinal obstruction (OR 0.75, 95% CI 0.34–1.65).

S-pouch vs. W-pouch

Four observational studies with control groups and 186 participants analyzed the comparison. No differences were reported, regarding dehiscence or stricture of the anastomosis (OR 1.05, 95% CI 0.26–4.23 and OR 2.74, 95% CI 0.94–7.99), wound infection or pelvic sepsis (OR 0.82, 95% CI 0.25–2.64 and OR 3.00, 95% CI 0.45–20.07), ileal pouch fistula (OR 0.86, 95% CI 0.21–3.56), intestinal obstruction (OR 1.20, 95% CI 0.35–4.17), or ischemia or bleeding of the ileal pouch (OR 4.86, 95% CI 0.19–127.52 and OR 1.02, 95% CI 0.15–6.68).

K-pouch vs. S-pouch

An observational study with control group and 136 participants made the comparison. The patients with the K-pouch had a lower incidence of failure (OR 0.21, 95% CI 0.07—0.66), compared with the S-pouch.

K-pouch vs. W-pouch

An observational study with control group and 386 participants made the comparison. There was no difference in the frequency of failure (OR 1.03, 95% CI 0.37–2.89).

Modified two-stage restorative proctocolectomy with ileal pouch and ileal-anal anastomosis

Recommendation No. 39: Two-stage restorative proctocolectomy is recommended in patients with UC that is refractory to medical treatment, when the patient has not received therapy with steroids or anti-TNF drugs during the six weeks prior to the intervention. Conditional, in favor of the strategy. Quality of evidence ⊕◯◯◯.

Good practice point: Two-stage restorative proctocolectomy can also be considered for managing patients with refractory UC that present with adequate nutritional status. Conditional, in favor of the strategy. Quality of evidence ⊕◯◯◯.

A systematic review[55] compared the use of two-stage proctocolectomy with ileal pouch-anal anastomosis compared with the same procedure in three stages, in patients with UC. The three-stage procedure did not reduce the incidence of anastomotic leaks (OR 0.98, 95% CI 0.39–2.45), surgical wound infection (OR 1.01, 95% CI 0.70–1.47), the development of pouchitis (OR 0.98, 95% CI 0.55–1.76), or anastomotic stricture (OR 0.65, 95% CI 0.35–1.20).

Preoperative anti-TNF as a risk factor for developing surgical site infection

Recommendation No. 40: Three-stage restorative proctocolectomy is recommended in patients with UC that is refractory to medical treatment, when the patient has received therapy with steroids or biologics during the period prior to the intervention. Conditional, in favor of the strategy. Quality of evidence ⊕◯◯◯.

Good practice point: Three-stage restorative proctocolectomy can also be considered for managing patients with medical treatment-refractory UC that present with anemia or malnutrition.

A systematic review[56] analyzed the effect of using anti-TNF medications in patients with UC during the preoperative period. The patients exposed to anti-TNFs had a higher frequency of surgical site infection, when the medication was administered within four weeks before the intervention (OR 8.76, 95% CI 1.53–50.13), without the apparent persistence of risk, when the medication was applied beyond that time window (OR 2.42, 95% CI 0.25–23.81 and OR 0.74, 95% CI 0.14–3.87 within 8 and 12 weeks). Exposure to anti-TNF drugs did not increase the frequency of anastomotic leaks, regardless of the preoperative time window at which the treatment was applied (OR 0.54, 95% CI 0.21–1.38 within 4 weeks; OR 0.54, 95% CI 0.08–3.61 within 8 weeks, and OR 0.54, 95% CI 0.21–1.38 within 12 weeks).

Postoperative complication risk in patients exposed to pharmacologic interventions

A systematic review[57] reported the effect of exposure to pharmacologic therapies for managing UC, in patients that underwent major abdominal surgery.

Exposure to steroids

Steroid exposure consisted of their administration for a period of more than 10 days, during the 30 days prior to the procedure. Steroid use resulted in a greater incidence of postoperative infection (OR 1.49, 95% CI 1.10–2.02) and intra-abdominal complications (OR 1.53 95% CI 1.28–1.84).

Previous exposure to 5-ASA

Exposure consisted of the use of oral or topical mesalamine, balsalazide, olsalazine, or sulfasalazine for a period of more than 10 days, during the 30 days prior to the procedure. The patients that received 5-ASA did not have a higher incidence of postoperative infection (OR 0.50, 95% CI 0.26—0.96) or intra-abdominal complications (OR 0.77, 95% CI 0.45–1.33).

Previous exposure to immunosuppressants

Exposure consisted of the use of azathioprine, 6-mercaptopurine, methotrexate, cyclosporine, or tacrolimus for one month prior to the procedure. The patients that used immunosuppressants did not have a higher incidence of postoperative infection (OR 1.10, 95% CI 0.86–1.39), surgical site infection (OR 1.35. 95% CI 0.96–1.89) or extra-abdominal infection (OR 1.17, 95% CI 0.80–1.71), nor did perioperative exposure to immunosuppressants increase the incidence of intra-abdominal complications (OR 0.86, 95% CI 0.66–1.12).

Previous exposure to anti-TNFs

Exposure consisted of the use of adalimumab, golimumab, and infliximab, for a period of four to 12 weeks prior to the procedure. The patients that used anti-TNFs had a higher incidence of postoperative infection (OR 1.26, 95% CI 1.03–1.53) and intra-abdominal complications (OR 1.38, 95% CI 1.04–1.82), without increasing the frequency of surgical site infection (OR 1.18, 95% CI 0.83–1.68) or extra-abdominal infection (OR 1.34, 95% CI 0.96–1.87).

Previous exposure to anti-integrins

Exposure consisted of the use of vedolizumab, for a period of 12–16 weeks prior to the procedure. Anti-integrin use did not produce a higher incidence of postoperative infection (OR 0.61, 95% CI 0.28–1.36), surgical site infection (OR 1.64, 95% CI 0.77–3.50), or extra-abdominal infection (OR 1.15, 95% CI 0.43–3.08), nor did perioperative anti-integrin exposure increase the incidence of intra-abdominal complications (OR 0.40, 95% CI 0.14–1.20).

Ethical considerations

The present review is considered no risk because its primary source of information was published and unpublished studies. It did not need approval from an ethics committee, given that no interventions, procedures, clinical history reviews, or interviews were required for producing the article. The present document contains no photographs or sensitive data that could breach data confidentiality and complies with the current bioethical research regulations.

Financial disclosure

These guidelines were funded by the Pan American Crohn's and Colitis Organisation (PANCCO). The developer group formulated the recommendations, and the managing body did not influence their content.

Conflict of interest

Maria Luisa Jara Alba has received fees from AbbVie; Cyrla Zaltman has received funds from AbbVie, Janssen, and Pfizer; Teresa Andara is a speaker and consultant for Janssen and AbbVie laboratories; Maria Teresa Galiano de Sánchez has received fees from Takeda and AbbVie; Esther Torres has participated in clinical studies, educational donations, and research collaborations with AbbVie, Tigenix, and Talceda; Maria Carolina Miranda has received fees from Ferrer; Beatriz Iade has received funds from Janssen, AbbVie, and Pfizer; Alicia Sambuelli has received funds from AbbVie, Takeda, Janssen, and Biotoscana; Socrates Bautista has received fees from AbbVie; Paulo Gustavo Kotze has received fees from Takeda, AbbVie, Janssen, and Pfizer; Martin Ariel Toro has received fees from AbbVie and Takeda; Juan de Paula has received fees from AbbVie, Janssen, Takeda, Roche, and Pfizer; Josue Barahona Garrido has received fees from Takeda and Janssen; Jesus Kazuo Yamamoto Furusho has received benefits from Takeda, Alfasigma, and Janssen; Ivan Ramos has received funds from Janssen and Pfizer; Ignacio Alfaro has received fees from AbbVie and Janssen, Giovanny Avelar has received funds from Mon-

naie and AbbVie; Flavio Steinwurz has received funds from Takeda, Sandoz, and Janssen; Fabian Juliao has received funds from AbbVie, Novartis, Pfizer, Novamed, Takeda, and Broppas; Kenneth Ernest has received fees from Janssen, AbbVie, Ferring, AstraZeneca, Takeda, Menarini, and Pfizer; Guillermo Otoya has received fees from Janssen and FALK; Francisco Bosques has received fees from Janssen; and Guillermo Rafael Veitia Velasquez has received fees from Celltrion.

C.F. Grillo-Ardila, Patricio-Ibañez, R. Ortuño-Escalante, F.N. Piñol-Jiménez, M.T. Vallejo-Ortega, J.I. Torres-Castillo, C. Hamon-Pinilla, C.H. Calderon-Franco, and A.M. Escobar-Villegas all declare there is no conflict of interest.

References

1. Ungaro R, Mehandru S, Allen PB, et al. Ulcerative colitis. Lancet. 2017;389:1756–70, http://dx.doi.org/10.1016/S0140-6736(16)32126-2.
2. Monstad IL, Solberg IC, Cvancarova M, et al. Outcome of ulcerative colitis 20 years after diagnosis in a prospective population-based inception cohort from south-eastern Norway, the IBSEN study. J Crohns Colitis. 2021;15:969–79, http://dx.doi.org/10.1093/ecco-jcc/jjaa232.
3. Kaplan GG, Ng SC. Understanding and preventing the global increase of inflammatory bowel disease. Gastroenterology. 2017;152:313–21, http://dx.doi.org/10.1053/j.gastro.2016.10.020, e2.
4. Kotze PG, Underwood FE, Damião AOMC, et al. Progression of inflammatory bowel diseases throughout Latin America and the Caribbean: a systematic review. Clin Gastroenterol Hepato. 2020;18:304–12, http://dx.doi.org/10.1016/j.cgh.2019.06.030.
5. Yamamoto-Furusho JK, Sarmiento-Aguilar A, Toledo-Mauriño JJ, et al. Incidence and prevalence of inflammatory bowel disease in Mexico from a nationwide cohort study in a period of 15 years (2000–2017). Medicine (Baltimore). 2019;98:e16291, http://dx.doi.org/10.1097/MD.0000000000016291.
6. Juliao-Baños F, Kock J, Arrubla M, et al. Trends in the epidemiology of inflammatory bowel disease in Colombia by demographics and region using a nationally representative claims database and characterization of inflammatory bowel disease phenotype in a case series of Colombian patients. Medicine (Baltimore). 2021;100:e24729, http://dx.doi.org/10.1097/MD.0000000000024729.
7. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular, and serological classification of inflammatory bowel disease: report of a working party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol. 2005;19:5A–36A, http://dx.doi.org/10.1155/2005/269076.
8. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG clinical guideline: ulcerative colitis in adults. Am J Gastroenterol. 2019;114:384–413, http://dx.doi.org/10.14309/ajg.0000000000000152.
9. Lönnfors S, Vermeire S, Greco M, et al. IBD and health-related quality of life - discovering the true impact. J Crohns Colitis. 2014;8:1281–6, http://dx.doi.org/10.1016/j.crohns.2014.03.005.
10. Tsai L, Nguyen NH, Ma C, et al. Systematic review and meta-analysis: risk of hospitalization in patients with ulcerative colitis and Crohn's disease in population-based cohort studies. Dig Dis Sci. 2021, http://dx.doi.org/10.1007/s10620-021-07200-1.
11. Tsai L, Ma C, Dulai PS, et al. Contemporary risk of surgery in patients with ulcerative colitis and Crohn's disease: a meta-analysis of population-based cohorts. Clin Gastroenterol Hepatol. 2021;19:2031–45, http://dx.doi.org/10.1016/j.cgh.2020.10.039, e11.
12. Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: an update on the selecting therapeutic targets in inflammatory bowel disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): determining therapeutic goals for Treat-to-Target strategies in IBD. Gastroenterology. 2021;160:1570–83.
13. Ministerio de Salud y la Protección Social - MinSalud. Guía Metodológica para la elaboración de Guías de Práctica Clínica con Evaluación Económica en el Sistema General de Seguridad Social; 2012. p. 1–312. Disponible en: https://www.iets.org.co/Archivos/79/Guia_actualizacion_V10_06092017-2.pdf.
14. Organización Panamericana de la Salud (OPS). Directriz para el fortalecimiento de los programas nacionales de guías informadas por la evidencia; 2018. p. 1–92. Disponible en: https://iris.paho.org/bitstream/handle/10665.2/49145/9789275320167_spa.pdf?sequence=5&isA.
15. Grillo-Ardila CF, Mogollón-Mariño AC, Amaya-Guío J, et al. Guía de práctica clínica para la prevención de eventos tromboembólicos venosos durante la gestación, el parto o el puerperio. Rev Colomb Obstet Ginecol. 2017;68:286–304. Disponible en: https://revista.fecolsog.org/index.php/rcog/article/view/3084.
16. Grupo Desarrollador del Consenso de Tromboprofilaxis en Cirugía Ginecológica, Federación Colombiana de Obstetricia y Ginecología (FECOLSOG). Consenso de tromboprofilaxis en cirugía ginecológica. Rev Colomb Obstet Ginecol. 2021;72:53–8. Disponible en: https://revista.fecolsog.org/index.php/rcog/article/view/3666.
17. Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions. 2nd edition John Wiley & Sons; 2019. p. 1–692. ISBN 9781119536611.
18. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008, http://dx.doi.org/10.1136/bmj.j4008.
19. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898, http://dx.doi.org/10.1136/bmj.l4898.
20. GRADEpro GDT: GRADEpro. Guideline development tool [Internet]. McMaster University and Evidence Prime, 2021. Disponible en: gradepro.org.
21. Brożek JL, Akl EA, Alonso-Coello P, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. Allergy. 2009;64:669–77, http://dx.doi.org/10.1111/j.1398-9995.2009.01973.x.
22. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924–6, http://dx.doi.org/10.1136/bmj.39489.470347.AD.
23. Marshall JK, Thabane M, Steinhart AH, et al. Rectal 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2010;1:CD004115, http://dx.doi.org/10.1002/14651858.CD004115.pub2.
24. Murray A, Nguyen TM, Parker CE, et al. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2020;8:CD000543, http://dx.doi.org/10.1002/14651858.CD000543.pub5.
25. Ford AC, Bernstein CN, Khan KJ, et al. Glucocorticosteroid therapy in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol. 2011;106:590–9, http://dx.doi.org/10.1038/ajg.2011.70.
26. Sherlock ME, MacDonald JK, Griffiths AM, et al. Oral budesonide for induction of remission in ulcerative col-

itis. Cochrane Database Syst Rev. 2015;10:CD007698, http://dx.doi.org/10.1002/14651858.CD007698.pub3.
27. Nguyen NH, Fumery M, Dulai PS, et al. Comparative efficacy and tolerability of pharmacological agents for management of mild to moderate ulcerative colitis: a systematic review and network meta-analyses. Lancet Gastroenterol Hepatol. 2018;3:742–53, http://dx.doi.org/10.1016/S2468-1253(18)30231-0.
28. Shibolet O, Regushevskaya E, Brezis M, et al. Cyclosporine A for induction of remission in severe ulcerative colitis. Cochrane Database Syst Rev. 2005;1:CD004277, http://dx.doi.org/10.1002/14651858.CD004277.pub2.
29. Lasa J, Olivera P. Efficacy of tacrolimus for induction of remission in patients with moderate-to-severe ulcerative colitis: a systematic review and meta-analysis. Arq Gastroenterol. 2017;54:167–72, http://dx.doi.org/10.1590/s0004-2803.201700000-15.
30. Gisbert JP, Linares PM, McNicholl AG, et al. Meta-analysis: the efficacy of azathioprine and mercaptopurine in ulcerative colitis. Aliment Pharmacol Ther. 2009;30:126–37, http://dx.doi.org/10.1111/j.1365-2036.2009.04023.x.
31. Chande N, Wang Y, MacDonald JK, et al. Methotrexate for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2014:CD006618, http://dx.doi.org/10.1002/14651858.CD006618.pub3.
32. Limketkai BN, Iheozor-Ejiofor Z, Gjuladin-Hellon T, et al. Dietary interventions for induction and maintenance of remission in inflammatory bowel disease. Cochrane Database Syst Rev. 2019;2:CD012839, http://dx.doi.org/10.1002/14651858.CD012839.pub2.
33. Caldeira L de F, Borba HH, Tonin FS, et al. Fecal microbiota transplantation in inflammatory bowel disease patients: a systematic review and meta-analysis. PLoS One. 2020;15:e0238910, http://dx.doi.org/10.1371/journal.pone.0238910.
34. Kafil TS, Nguyen TM, MacDonald JK, et al. Cannabis for the treatment of ulcerative colitis. Cochrane Database Syst Rev. 2018;11:CD012954, http://dx.doi.org/10.1002/14651858.CD012954.
35. Khan KJ, Ullman TA, Ford AC, et al. Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis. Am J Gastroenterol. 2011;106:661–73, http://dx.doi.org/10.1038/ajg.2011.72.
36. Guo C, Wu K, Liang X, et al. Infliximab clinically treating ulcerative colitis: a systematic review and meta-analysis. Pharmacol Res. 2019;148:104455, http://dx.doi.org/10.1016/j.phrs.2019.104455.
37. Choy MC, Seah D, Faleck DM, et al. Systematic review and meta-analysis: optimal salvage therapy in acute severe ulcerative colitis. Inflamm Bowel Dis. 2019;25:1169–86, http://dx.doi.org/10.1093/ibd/izy383.
38. Narula N, Marshall JK, Colombel J-F, et al. Systematic review and meta-analysis: infliximab or cyclosporine as rescue therapy in patients with severe ulcerative colitis refractory to steroids. Am J Gastroenterol. 2016;111:477–91, http://dx.doi.org/10.1038/ajg.2016.7.
39. Zhang ZM, Li W, Jiang XL. Efficacy and safety of adalimumab in moderately to severely active cases of ulcerative colitis: a meta-analysis of published placebo-controlled trials. Gut Liver. 2016;10:262–74, http://dx.doi.org/10.5009/gnl15042.
40. Bickston SJ, Behm BW, Tsoulis DJ, et al. Vedolizumab for induction and maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2014:CD007571, http://dx.doi.org/10.1002/14651858.CD007571.pub2.
41. Ebada MA, Elmatboly AM, Ali AS, et al. An updated systematic review and meta-analysis about the safety and efficacy of infliximab biosimilar, CT-P13, for patients with inflammatory bowel disease. Int J Colorectal Dis. 2019;34:1633–52, http://dx.doi.org/10.1007/s00384-019-03354-7.
42. Gisbert JP, Marín AC, McNicholl AG, et al. Systematic review with meta-analysis: the efficacy of a second anti-TNF in patients with inflammatory bowel disease whose previous anti-TNF treatment has failed. Aliment Pharmacol Ther. 2015;41:613–23, http://dx.doi.org/10.1111/apt.13083.
43. Singh S, Murad MH, Fumery M, et al. First- and second-line pharmacotherapies for patients with moderate to severely active ulcerative colitis: an updated network meta-analysis. Clin Gastroenterol Hepatol. 2020;18:2179–91, http://dx.doi.org/10.1016/j.cgh.2020.01.008, e6.
44. Murray A, Nguyen TM, Parker CE, et al. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2020;8:CD000544, http://dx.doi.org/10.1002/14651858.CD000544.pub5.
45. Timmer A, Patton PH, Chande N, et al. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2016;2016:CD000478, http://dx.doi.org/10.1002/14651858.CD000478.pub4.
46. Iheozor-Ejiofor Z, Kaur L, Gordon M, et al. Probiotics for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2020;3:CD007443, http://dx.doi.org/10.1002/14651858.CD007443.pub3.
47. Garg SK, Ahuja V, Sankar MJ, et al. Curcumin for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2012;10:CD008424, http://dx.doi.org/10.1002/14651858.CD008424.pub2.
48. Davies SC, Hussein IM, Nguyen TM, et al. Oral Janus kinase inhibitors for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2020;1:CD012381, http://dx.doi.org/10.1002/14651858.CD012381.pub2.
49. Huguet M, Pereira B, Goutte M, et al. Systematic review with meta-analysis: anti-TNF therapy in refractory pouchitis and Crohn's disease-like complications of the pouch after ileal pouch-anal anastomosis following colectomy for ulcerative colitis. Inflamm Bowel Dis. 2018;24:261–8, http://dx.doi.org/10.1093/ibd/izx049.
50. Kjær MD, Qvist N, Nordgaard-Lassen I, et al. Adalimumab in the treatment of chronic pouchitis. A randomized double-blind, placebo-controlled trial. Scand J Gastroenterol. 2019;54:188–93, http://dx.doi.org/10.1080/00365521.2019.1569718.
51. Ribaldone DG, Pellicano R, Saracco GM, et al. Vedolizumab for treatment of chronic refractory pouchitis: a systematic review with pool analysis. Rev Esp Enferm Dig. 2020;112:59–63, http://dx.doi.org/10.17235/reed.2019.6336/2019.
52. Lovegrove RE, Constantinides VA, Heriot AG, et al. A comparison of hand-sewn versus stapled ileal pouch anal anastomosis (IPAA) following proctocolectomy: a meta-analysis of 4183 patients. Ann Surg. 2006;244:18–26, http://dx.doi.org/10.1097/01.sla.0000225031.15405.a3.
53. Ahmed Ali U, Keus F, Heikens JT, et al. Open versus laparoscopic (assisted) ileo pouch anal anastomosis for ulcerative colitis and familial adenomatous polyposis. Cochrane Database Syst Rev. 2009;1:CD006267.
54. Simillis C, Afxentiou T, Pellino G, et al. A systematic review and meta-analysis comparing adverse events and functional outcomes of different pouch designs after restorative proctocolectomy. Colorectal Dis. 2018;20:664–75, http://dx.doi.org/10.1111/codi.14104.
55. Luo WY, Singh S, Cuomo R, et al. Modified two-stage restorative proctocolectomy with ileal pouch-anal anastomosis for ulcerative colitis: a systematic review and meta-analysis of observational research. Int J Colorectal Dis. 2020;35:1817–30, http://dx.doi.org/10.1007/s00384-020-03696-7.

56. Qiu Y, Zheng Z, Liu G, et al. Effects of preoperative anti-tumour necrosis factor alpha infusion timing on postoperative surgical site infection in inflammatory bowel disease: a systematic review and meta-analysis. United European Gastroenterol J. 2019;7:1198–214, http://dx.doi.org/10.1177/2050640619878998.

57. Law CCY, Bell C, Koh D, et al. Risk of postoperative infectious complications from medical therapies in inflammatory bowel disease. Cochrane Database Syst Rev. 2020;10:CD013256, http://dx.doi.org/10.1002/14651858.CD013256.pub2.