ULCERATIVE COLITIS

CHI Formulary Development Project

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM- September 2023

To the CHI Original Ulcerative colitis Clinical Guidance- Issued January 2020

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- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

Abbreviations

5-ASA	5-Aminosalicylic Acid
AGA	American Gastroenterological Association
ASC	Acute Severe Colitis
ASUC	Acute severe ulcerative colitis
BDP	Beclomethasone Dipropionate
CADTH	Canadian Agency for Drugs and Technologies in Health
CHI	Council of Health Insurance
CPG	Clinical Practice Guideline
ECCO	European Crohn's and Colitis Organisation
EMA	European Medicines Agency
EU	Emergency Use
FDA	Food and Drug Administration
GI	Gastrointestinal
HAS	Haute Autorite de Sante
HTA	Health Technology Assessment
IBD	Irritable Bowel Disease
ICER	Incremental Cost-Effectiveness Ratio
IDF	Insurance Drug Formulary
IFX	Infliximab
IG-IBD	Italian Group – Irritable Bowel Disease
IPAA	Ileal Pouch-Anal Anastomosis
IQWIG	Institute for Quality and Efficiency in Health Care
IV	Intravenous
N/A	Not Available
NICE	National Institute for Health and Care Excellence
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PA	Prior Authorization

PBAC	Pharmaceutical Benefits Advisory Committee
PUCAI	Pediatric Ulcerative Colitis Activity Index
QALY	Quality-Adjusted Life-Year
SFDA	Saudi Food and Drug Authority
ST	Step Therapy
SUBQ	Subcutaneous
TNF-alpha	Tumor Necrosis Factor-alpha
UC	Ulcerative Colitis

Executive Summary

Ulcerative colitis (UC), an inflammatory bowel disease (IBD), is characterized by persistent inflammation and the formation of ulcers in the inner lining of the large intestine. This chronic condition is a result of the immune system's abnormal responses. Although UC can occur at any point in life, it tends to be more prevalent among individuals aged 15 to 30. The symptoms of ulcerative colitis can differ from individual to individual, and may consist of diarrhea, the presence of blood in the stool, and abdominal pain[1].

UC symptoms can vary, depending on the severity of inflammation and its location. The symptoms comprise: diarrhea, frequently accompanied by blood or pus, rectal bleeding, abdominal pain, and cramps, feeling an urgent need to defecate, weight loss, fatigue, and fever. In children it can lead to inadequate growth. Most individuals with ulcerative colitis experience mild to moderate symptoms[2].

In patients with Crohn's disease, segments of the intestine that are unaffected are interspersed among areas of inflammation. Conversely, UC involves constant inflammation of the colon. Notably, UC targets solely the innermost lining of the colon, whereas Crohn's disease can involve all the layers of the intestinal walls[3].

Endoscopy of the large intestine, alongside biopsies, is a means to diagnose UC and exclude other gastrointestinal conditions. This procedure also aids in gauging the extent of ulcerative colitis and the portion of the large intestine that is impacted. Two types of endoscopies are commonly employed for diagnosing ulcerative colitis: Colonoscopy to visualize the lining of both the rectum and the entire colon and flexible sigmoidoscopy to visualize the lining of the rectum and the lower colon[4].

UC affects approximately 1 million individuals in the United States. The annual incidence rate ranges from 10.4 to 12 cases per 100,000 people, while the prevalence rate is estimated to be between 35 and 100 cases per 100,000 people[5].

The estimated annual prevalence of UC in the general population in Saudi Arabia is between 7.6 and 245 cases per 100,000 individuals[6].

The main objective in the treatment of UC is to assist patients in better regulating their immune system. Although there is currently no known cure for UC and the possibility of flare-ups recurring exists, a combination of treatment approaches can aid in managing the condition and enabling individuals to lead fulfilling lives. The treatment of UC involves a multifaceted approach, which encompasses medication usage, participation in clinical trials, dietary and nutritional modifications, and, in certain cases, surgical interventions aimed at repairing or removing affected sections of the gastrointestinal (GI) tract[7].

CHI issued ulcerative colitis clinical guidance after thorough review of renowned international and national clinical guidelines in January 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an addendum to the prior CHI Ulcerative colitis clinical guidance and seeks to offer guidance for the effective management of Ulcerative Colitis. It provides an **update on the Ulcerative Colitis Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized, by being the addition of two new SFDA registered drugs **Ustekinumab** and **Upadacitinib** and one new non-SFDA registered drugs: **Ozanimod** (approved by the FDA in May 2021 for adults with moderately to severely active UC). **Etrasimod**, an oral sphingosine 1-phosphate (S1P) receptor modulator, is under investigation for treating adults with moderate to severe ulcerative colitis. FDA and EMA accepted the regulatory submissions of Etrasimod in December 2022.

Moreover, **new guidelines are added to the report** such as the Saudi Arabia consensus guidance for the diagnosis and management of adults with inflammatory bowel disease **2022,** the American Gastroenterological Association (AGA) clinical guideline on the management of moderate to severe ulcerative colitis **2020**, the clinical guidelines for the management of inflammatory bowel disease: update of a French national consensus **2020**, the IG-IBD clinical guidelines based on the GRADE methodology **2022,** and the Management of Pediatric Ulcerative Colitis, **Ambulatory** Care-An Evidence-based Guideline from European Crohn's and Colitis Organization and European Society of Pediatric Gastroenterology, Hepatology and Nutrition **2018** and the Management of Pediatric Ulcerative Colitis, **Part 2**: Acute **Severe** Colitis—An Evidence-based Consensus Guideline From the European Crohn's and Colitis

Organization and the European Society of Pediatric Gastroenterology, Hepatology and Nutrition **2018** and the ECCO guidelines on therapeutics in Ulcerative colitis divided into two parts: medical treatment and surgical treatment **2021**.

After carefully examining clinical guidelines and reviewing the SFDA drug list, it is advisable to include the SFDA registered drug **Ustekinumab** (STELARA ®) and **Upadacitinib** (RINVOQ®) in the CHI formulary while changing some related prescribing edits to previously listed drugs in the January 2020 CHI report which are: Azathioprine does not need "Prior Authorization (PA)" and "Emergency Use (EU)" as a prescribing edit (PE): it is used as an adjunctive therapy and can be administered orally. Cyclosporin has a "Step Therapy (ST)" PE: it should be used in hospitalized adult patients with acute severe ulcerative colitis refractory to intravenous corticosteroids, the AGA suggests using infliximab or cyclosporine. Budesonide has a "ST" PE: it may be considered in patients with mild disease refractory to 5-aminosalicylic acid (5-ASA) before oral prednisolone. Tofacitinib has a "ST" PE: it should be considered as a second-line treatment in adult outpatients with moderate-to-severe UC who failed biologic agents. There have been no withdrawn drugs since January 2020.

Main recommendations issued by different Health Technology Assessment (HTA) bodies on the use of the current medications in UC were reviewed and summarized. These include the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC).

Table 1. Addition of New SFDA Registered Drugs for the Management of Ulcerative Colitis

MAJOR CHANGES		
Addition of New Molecules	**Drug Class**	**HTA Recommendations**
Ustekinumab	Monoclonal antibody- interleukin inhibitor	Positive recommendations from CADTH (2020)[8], NICE (2020)[9] and PBAC (2022)[10]. No added value from HAS (2020)[11] .N/A for IQWIG.
Upadacitinib	Janus Kinase (JAK) Inhibitors	Positive recommendations from NICE (2023)[12] and PBAC (2023)[13] . In process for CADTH. No added clinical value for HAS (2023)[14]. N/A for IQWIG.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in the Ulcerative colitis management.

Below is a table summarizing the major changes based on the different ulcerative colitis guidelines used to issue this report:

Table 2. General Recommendations for the Management of Ulcerative Colitis

Management of Ulcerative Colitis	
General Recommendations	**Level of Evidence/Grade of Recommendation and reference**
Oral and/or topical 5-ASA derivatives are recommended as first-line treatment for the induction and maintenance of remission in mild-to-moderate UC.	Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed)[15]
Oral budesonide is recommended over conventional oral corticosteroids to induce remission in UC. If conventional oral corticosteroids are used, the patient should be advised about common and serious side effects of corticosteroids.	Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed)[15]
Thiopurines are recommended to maintain remission in patients with UC who are corticosteroid resistant or corticosteroid dependent.	Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed)[15]
In patients with moderately active UC who have failed conventional therapy, treatment with biological therapies, i.e., infliximab, golimumab, adalimumab, vedolizumab, or ustekinumab is recommended.	Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed)[15]

Ustekinumab for induction and maintenance of remission in patients with moderate-to-severely active UC is recommended.	Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed)[15]
Ozanimod for induction and maintenance of remission in UC following failure of conventional and/or advanced therapies is recommended.	Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed)[15]
Upadacitinib for induction and maintenance of remission in UC following failure of conventional and/or advanced therapies is recommended.	Quality of evidence: High; GRADE: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed)[15]
Infliximab, golimumab, adalimumab, vedolizumab, ustekinumab, ozanimod, upadacitinib, or tofacitinib are recommended for UC patients on high-dose 5-ASA maintenance therapy requiring two or more courses of corticosteroids in the preceding year or who developed corticosteroid dependence or refractory condition.	Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed)[15]
If disease relapse occurs with ustekinumab therapy, dose escalation (typically by decreasing the dosing interval to every 4 weeks) should be considered while evaluating for co-existing or exacerbating factors.	Quality of evidence: Moderate; Grade: Moderate. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed)[15]
<u>Management of hospitalized patients:</u> In hospitalized adult patients with acute severe ulcerative colitis, the AGA suggests using intravenous methylprednisolone dose equivalent of 40 to 60mg/d rather than higher dose intravenous corticosteroids.	Conditional recommendation, very low-quality evidence[16]

Management of hospitalized patients: In hospitalized adult patients with acute severe ulcerative colitis refractory to intravenous corticosteroids, the AGA suggests using infliximab or cyclosporine.	Conditional recommendation, low quality evidence[16]
For adults with moderate to severe UC refractory to at least one biologic, IG-IBD recommends using tofacitinib or ustekinumab for the induction of remission.	Strong recommendation; moderate-quality evidence for tofacitinib; low-quality evidence for ustekinumab – Agreement rate: 91%)[17]
For pediatric population-ambulatory setting: Second-generation oral steroids with lower systemic effect such as beclomethasone dipropionate (BDP) and budesonide-MMX (the evidence for budesonide-MMX is supportive only for left-sided colitis) may be considered in patients with mild disease refractory to 5-ASA before oral prednisolone.	93% agreement[18]
For pediatric population- ambulatory setting: Thiopurines are recommended for maintaining remission in children who are corticosteroid-dependent or relapsing frequently (>2 relapses per year) despite optimal 5-ASA treatment and in 5-ASA intolerant patients.	N/A[18]
For pediatric population- ambulatory setting: Thiopurines should not be used for induction of remission in pediatric UC patients.	100% agreement[18]
For pediatric population- ambulatory setting: Infliximab (IFX) should be considered in chronically active or steroid-dependent UC, uncontrolled by 5-ASA and thiopurines, for both induction and maintenance of remission.	100% agreement[18]
For pediatric population- ambulatory setting: Adalimumab or golimumab could be considered in those who initially respond but then lose response or are intolerant to IFX, based on serum levels and antibodies.	95% agreement[18]
For pediatric population- severe colitis: Pain management	98% agreement[19]

Opiates should be used exceptionally with caution and close monitoring, in doses equivalent to 0.1 mg/ kg morphine, given the remote risk of facilitating megacolon.	
<u>For pediatric population- severe colitis:</u> Nutritional support Regular diet should be continued in most ASC cases. Enteral (or parenteral in those not tolerating enteral) nutrition may be used if oral feeding is not tolerated or in malnutrition.	98% agreement[19]
<u>For pediatric population- severe colitis:</u> A PUCAI >45 points on the third day of IVCS treatment should dictate planning for second-line therapy between days 3 to 5.	100% agreement[19]
<u>For pediatric population- severe colitis:</u> Second-line therapy should be initiated on the fifth day of IVCS treatment in children with a PUCAI >65 points.	100% agreement [19]
<u>For pediatric population- severe colitis:</u> IVCS should be continued for an additional 2 to 5 days in children with a PUCAI of 35 to 65 on day 5; daily monitoring for confirming gradual response is recommended before a decision on second-line therapy is made in most cases within a total of 7 to 10 days of treatment.	100% agreement [19]
<u>For pediatric population- severe colitis:</u> <u>When steroids fail:</u> Infliximab is recommended as the second-line medical therapy for anti-TNF naive children failing IVCS	100% agreement [19]
<u>For pediatric population- severe colitis:</u> <u>When steroids fail:</u> Calcineurin inhibitors (tacrolimus and cyclosporine) can be considered as an alternative second-line medical therapy.	100% agreement [19]
<u>For pediatric population- severe colitis:</u> <u>When steroids fail:</u>	100% agreement [19]

When introducing second-line therapy, the possibility of non-response and therefore need for colectomy must always be discussed (100% agreement).	

At the end of the report, a **key recommendation synthesis section** is added highlighting the latest updates in **ulcerative colitis clinical and therapeutic management.**

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

This section is divided into two parts: one part includes recommendations from **updated versions of guidelines** mentioned in the previous CHI ulcerative colitis report, and another part includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This section contains the **updated versions** of the guidelines mentioned in the January 2020 CHI Ulcerative colitis Report and the corresponding recommendations:

Table 3. Guidelines Requiring Revision

Guidelines requiring revision	
Old versions	**Updated versions**
The American College of Gastroenterology (ACG) Clinical Guideline: Ulcerative Colitis in Adults (22 February 2019)	N/A*
Ulcerative Colitis Management NICE Clinical Guidelines (2019)	N/A*
Clinical Practice Guidelines for the Medical Management of Non-hospitalized Ulcerative Colitis: The Toronto Consensus (2015)	N/A*

**: No updated version available: the existing version is the most recent one and no further updates or revisions have been made or released.*

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI Ulcerative colitis report, along with their recommendations.

Table 4. List of Additional Guidelines

Additional Guidelines
Saudi Arabia Consensus Guidance for the Diagnosis and Management of Adults with Inflammatory Bowel Disease (2022)[15]
ECCO Guidelines on Therapeutics in Ulcerative Colitis: Surgical Treatment (2021)[20]
ECCO Guidelines on Therapeutics in Ulcerative Colitis: Medical Treatment (2021)[21]
American Gastroenterological Association (AGA) Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis (2020)[16]
Clinical Guidelines for the Management of Inflammatory Bowel Disease: Update of a French National Consensus (2020)[22]
Use of Biologics and Small Molecule Drugs for the Management of Moderate to Severe Ulcerative Colitis: IG-IBD Clinical Guidelines Based on the GRADE Methodology (2022)[17]
Management of Pediatric Ulcerative Colitis, Ambulatory Care-An Evidence-Based Guideline from European Crohn's and Colitis Organization and European Society of Pediatric Gastroenterology, Hepatology and Nutrition (2018)[18]
Management of Pediatric Ulcerative Colitis, Part 2: Acute Severe Colitis—An Evidence-based Consensus Guideline from the European Crohn's and Colitis Organization and the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (2018)[19]

1.2.1 Saudi Arabia Consensus Guidance for the Diagnosis and Management of Adults with Inflammatory Bowel Disease (2022)

The recommendations of Saudi Arabia consensus guidance for the diagnosis and management of adults with inflammatory bowel disease 2022 are listed below[15]:

- **Oral** and/or **topical 5-ASA derivatives** are recommended as **first-line treatment** for the induction and maintenance of remission in mild-to-moderate UC. Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).
- Budesonide MMX topical and/or systemic corticosteroids are recommended for induction of remission in UC, in patients who failed to respond to mesalazine

derivatives. Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

- Oral budesonide is recommended over conventional oral corticosteroids to induce remission in UC. If conventional oral corticosteroids are used, the patient should be advised about common and serious side effects of corticosteroids. Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).
- Thiopurines are recommended to maintain remission in patients with UC who are corticosteroid resistant or corticosteroid dependent. Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).
- Vedolizumab is preferred over adalimumab to induce remission in moderate-to-severe ambulatory UC patients naïve to biologic agents. Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).
- In patients with moderately active UC who have failed conventional therapy, treatment with biological therapies, i.e., infliximab, golimumab, adalimumab, vedolizumab, or ustekinumab, is recommended. Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).
- Ustekinumab is recommended for induction and maintenance of remission in patients with moderate-to-severely active UC. Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).
- Ozanimod is recommended for induction and maintenance of remission in UC following failure of conventional and/or advanced therapies. Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).
- Upadacitinib is recommended for induction and maintenance of remission in UC following failure of conventional and/or advanced therapies. Quality of evidence: High; GRADE: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).
- Tofacitinib is recommended as a second-line treatment in adult outpatients with moderate-to-severe UC who failed biologic agents. Quality of evidence: High; Grade: High. Strength of recommendation: Strongly recommended (60% of panel strongly agreed).

- Tofacitinib is **not** recommended for patients with a history of thromboembolic disease, cardiovascular disease, or those ≥ 50 years old, with at least one cardiovascular risk factor, because of an increased risk of thromboembolic events. Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).
- Infliximab in combination with thiopurines is preferred over infliximab monotherapy in moderate-to-severe UC. There is insufficient evidence to recommend combining other biologic therapies with thiopurines. Quality of evidence: Moderate; Grade: Moderate. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).
- The guideline recommends "against" 5-ASA continuation for maintenance of remission in adult ambulatory patients with moderate-to-severe UC who have attained remission with the use of immunosuppressants and/or biologic agents or tofacitinib. Quality of evidence: Moderate; Grade: Moderate. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).
- The guideline recommends infliximab, golimumab, adalimumab, vedolizumab, ustekinumab, ozanimod, upadacitinib, or tofacitinib for UC patients on high-dose 5-ASA maintenance therapy requiring two or more courses of corticosteroids in the preceding year or who developed corticosteroid dependence or refractory condition. Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).
- Vedolizumab may be considered for patients ≥ 65 years old, patients with a history of a recent infection, and individuals at higher risk of infection or malignancy. Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).
- If disease relapse occurs with ustekinumab therapy, dose escalation (typically by decreasing the dosing interval to every 4 weeks) should be considered while evaluating for co-existing or exacerbating factors. Quality of evidence: Moderate; Grade: Moderate. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

1.2.2 ECCO Guidelines on Therapeutics in Ulcerative Colitis: Surgical Treatment (2021)

The European Crohn's and Colitis Organization (ECCO) published its updated guidelines for the management of UC in two parts. The first pertains to the surgical

management of UC and is detailed in this section[20], while the second discusses the medical treatment for UC and is detailed in section 1.2.3.

Table 5. ECCO 2021 Evidence Levels (EL)

Level	Therapy/Prevention, Etiology/Harm
1a	Systematic Review (with homogeneity) of Randomized Controlled Trials
1b	Individual randomized controlled trial (with narrow confidence interval)
1C	All or none
2a	Systematic review (with homogeneity) of cohort studies
2b	Individual cohort study (including low quality randomized controlled trial)
2c	Outcomes research: ecological studies
3a	Systematic review (with homogeneity) of case-control studies
3b	Individual case-control study
4	Case-series (and poor-quality cohort and case-control studies)

The main recommendations published by the ECCO guidelines are listed below:

- Intravenous corticosteroids as the initial standard treatment for adult patients with ASUC are recommended, as this treatment induces clinical remission and reduces mortality. (EL3)
- Either infliximab or cyclosporine should be used in adult patients with steroid-refractory ASUC. When choosing between these strategies, center experience and a plan for maintenance therapy after cyclosporine should be considered. (EL3)
- Third-line sequential rescue therapies with calcineurin inhibitors [cyclosporine or tacrolimus] in ASUC refractory to corticosteroid therapy may delay the need for colectomy but are associated with high rates of adverse events and should only be administered in specialized centers. (EL2a)
- Reconstructive surgery may be offered to refractory and corticosteroid-dependent patients and improves quality of life despite the risk of early and late complications [EL2b].
- Proctocolectomy with end-ileostomy is an alternative for some patients and has lower morbidity and comparable quality of life [EL3a]
- Prophylactic anticoagulation therapy in adult patients with active UC during hospitalization is recommended, considering the high risk of venous thromboembolism during UC flares [EL4]

- After total proctocolectomy for medically refractory UC, IPAA is the procedure of choice, but permanent end-ileostomy is also a reasonable option for some patients. A shared decision-making approach should be used to tailor procedure selection to the patient's preference [EL3]
- Laparoscopic surgery is the preferred approach to patients with medically refractory UC, as it is associated with lower intra- and postoperative morbidity, faster recovery, fewer adhesions and incisional hernias, shorter hospital length of stay, improved female fecundity, and better cosmesis. [EL2]
- Although associated with an increased risk of rectal dysplasia, cancer, and dysplasia or cancer recurrence, patients with UC and a minimally affected rectum can be offered the option of an ileo-rectal anastomosis. [EL4]

1.2.3 ECCO Guidelines on Therapeutics in Ulcerative Colitis: Medical Treatment (2021)

Table 6. ECCO 2021 Strengths of Recommendation

Certainty	Definition
Strong	We recommend
Weak	We suggest
High	The authors have a lot of confidence that the true effect is like the estimated effect
Moderate	The authors believe that the true effect is probably close to the estimated effect
Low	The true effect might be markedly different from the estimated effect
Very Low	The true effect is probably markedly different from the estimated effect

The main recommendations published by the ECCO 2021 guidelines regarding the medical treatment of UC are listed below[21]:

Medical management of mildly-to-moderately active UC

- 5-aminosalicylates at a dose of ≥2 g/ day [d] to induce remission in patients with mildly-to moderately active UC is recommended [strong recommendation, quality of evidence low]
- Topical [rectal] 5-ASA at a dose of ≥1 g/d for the induction of remission in active distal colitis is recommended. [strong recommendation, low-quality evidence]

- The use of oral 5-ASA [≥2 g/d] combined with topical [rectal] 5-ASA over oral 5-ASA monotherapy for induction of remission in adult patients with active UC of at least rectosigmoid extent is suggested. [weak recommendation; very low-quality evidence]
- Using topical [rectal] steroids for the induction of remission in patients with active distal colitis is recommended. [strong recommendation, very low-quality evidence]
- Treatment with topical [rectal] 5-ASAs over topical [rectal] steroids for induction of remission in patients with active distal UC [weak recommendation, very low quality of evidence]
- The use of colonic-release corticosteroids for induction of remission in patients with active mild to-moderate UC is suggested. [weak recommendation, low quality of evidence]
- The use of thiopurines as monotherapy for the induction of remission in patients with active UC is not suggested [weak recommendation, very low quality of evidence]

Maintenance of remission in mildly-to-moderately active UC

- The use of oral 5-ASA at a dose ≥2 g/day for maintenance of remission in UC patients [strong recommendation; very low quality of evidence] is recommended.
- The use of topical [rectal] 5-ASA for the maintenance of remission in patients with distal UC [weak recommendation, very low-quality evidence] is suggested.
- Monotherapy with thiopurines for the maintenance of remission in patients with steroid-dependent UC or who are intolerant to 5-ASA [strong recommendation, moderate quality of evidence] is recommended.

Medical management of moderately-to-severely active UC

- Oral prednisolone for induction of remission in non-hospitalized patients with moderately to-severely active UC is recommended [strong recommendation, very low quality of evidence]
- Treatment with anti-tumor necrosis factor [TNF] agents [infliximab, adalimumab, and golimumab] to induce remission in patients with moderate-to-severe UC who have inadequate response or intolerance to conventional therapy is recommended. [strong recommendation, moderate- quality evidence]
- Treatment with vedolizumab for the induction of remission in patients with moderately-to severely active UC who have inadequate response or intolerance

to conventional therapy is recommended [strong recommendation, low quality of evidence]

- Treatment with tofacitinib to induce remission in patients with moderate-to-severe UC who have inadequate response or intolerance to conventional therapy is recommended. [strong recommendation, moderate quality of evidence]
- Treatment with ustekinumab for the induction of remission in patients with moderately-to-severely active UC with inadequate response or intolerance to conventional therapy is recommended. [strong recommendation, moderate quality of evidence]

Maintenance of remission of moderately-to-severely active UC

- Anti-TNF agents [infliximab, adalimumab, or golimumab] for the maintenance of remission in patients with UC who responded to induction therapy with the same drug is recommended. [strong recommendation, high-quality evidence]
- Vedolizumab for maintenance of remission in patients with UC who responded to induction therapy with vedolizumab is recommended. [strong recommendation, moderate-quality evidence]
- The use of vedolizumab rather than adalimumab for the induction and maintenance of remission in patients with moderately-to-severely active ulcerative colitis is suggested. [weak recommendation, low level of evidence]
- Tofacitinib for maintaining remission in patients with UC who responded to induction therapy with tofacitinib is recommended. [strong recommendation, moderate quality of evidence]
- Ustekinumab for the maintenance of remission in patients with UC who responded to induction therapy with ustekinumab is recommended. [strong recommendation, moderate quality of evidence]

1.2.4 American Gastroenterological Association (AGA) Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis (2020)

The American Gastroenterological Association (AGA) published in 2020 its clinical practice guidelines on the management of moderate to severe UC, and the main recommendations are detailed below[16]:

- In adult outpatients with moderate-severe UC who are **naïve** to biologic agents, the AGA suggests using **infliximab** or **vedolizumab** rather than adalimumab, for **induction** of remission. (Conditional recommendation, moderate quality evidence)

- In adult outpatients with moderate-severe UC who have previously been exposed to infliximab, particularly those with primary non-response, the AGA suggests using ustekinumab or tofacitinib, rather than vedolizumab or adalimumab for induction of remission. (Conditional recommendation, low quality evidence)
- In adult outpatients with active moderate-severe UC, thiopurine monotherapy for INDUCTION of remission is **not** recommended. (Conditional recommendation, very low quality of evidence)
- In adult outpatients with moderate-severe UC in remission, the AGA suggests using thiopurine monotherapy, rather than no treatment, for MAINTENANCE of remission. (Conditional recommendation low quality of evidence)
- In adult outpatients with moderate-severe UC, methotrexate monotherapy for induction or maintenance of remission is not preferred. (Conditional recommendation, low quality evidence)
- In adult outpatients with active moderate-severe UC, the AGA suggests using biologic monotherapy (TNFα antagonists, vedolizumab, ustekinumab) rather than thiopurine monotherapy for INDUCTION of remission. (Conditional recommendation, low quality evidence)
- In adult outpatients with moderate-severe UC in remission, the AGA makes no recommendation in favor of, or against, using biologic monotherapy (TNFα antagonists, vedolizumab or ustekinumab), rather than thiopurine monotherapy for MAINTENANCE of remission. (No recommendation, knowledge gap)
- In adult outpatients with moderate-severe UC, combining TNFα antagonists, vedolizumab or ustekinumab with thiopurines or methotrexate, is preferred over biologic or thiopurine monotherapy. (Conditional recommendation, low quality evidence)
- In adult outpatients with moderate-severe UC, the AGA suggests early use of biologic agents with or without immunomodulator therapy, rather than gradual step up after failure of 5-aminosalicylates. (Conditional recommendation, very low-quality evidence)

Management of hospitalized patients:

- In hospitalized adult patients with acute severe UC, the AGA suggests using intravenous methylprednisolone dose equivalent of 40 to 60mg/d rather than higher dose intravenous corticosteroids. (Conditional recommendation, very low-quality evidence)

- In hospitalized adult patients with acute severe ulcerative colitis without infections, adjunctive antibiotics are not recommended. (Conditional recommendation, very low quality of evidence)
- In hospitalized adult patients with acute severe ulcerative colitis refractory to intravenous corticosteroids, the AGA suggests using infliximab or cyclosporine. (Conditional recommendation, low quality evidence).

1.2.5 Clinical Guidelines for the Management of Inflammatory Bowel Disease: Update of a French National Consensus (2020)

The following algorithm summarizes the treatment regimens that are commonly adopted within the scope of UC[22].

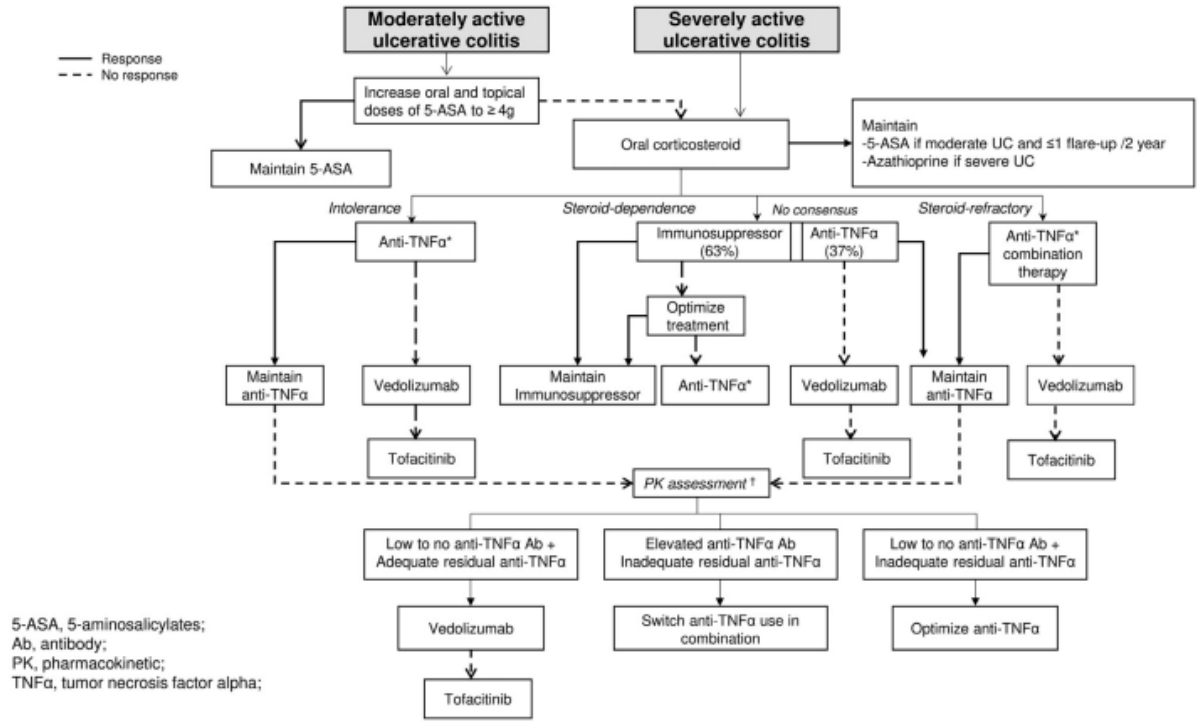

Figure 1. *Treatment algorithm for moderately or severely active ulcerative colitis. Adapted from Amiot A, Bouguen G, Bonnaud G, et al. Clinical guidelines for the management of inflammatory bowel disease: Update of a French national consensus. Digestive and Liver Disease. 2021;53(1):35-43. doi:10.1016/j.dld.2020.10.018.*

Moderately-to-severely active UC not requiring hospitalization:

- First-line treatment with oral 5-ASA ≥ 4 g per day plus topical 5-ASA for patients with moderate UC and oral corticosteroids for patients with moderate UC that did not respond to 5-ASA and those with severe UC. After induction of remission, maintenance therapy is indication using 5-ASA in case of moderate

UC with no more than one flare-up every 2 years and azathioprine in the other cases of moderate UC and severe UC.

1.2.6 IG-IBD Clinical Guidelines Based on the GRADE Methodology (2022)

The Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD) published its clinical guidelines in 2022 and the main recommendations are detailed below[17]:

- For adults with moderate to severe UC refractory to conventional therapy who are naïve to biologics, IG-IBD recommends using infliximab, adalimumab, golimumab, vedolizumab, ustekinumab or tofacitinib over no treatment to induce remission. (Strong recommendation; high-quality evidence for infliximab and adalimumab; moderate-quality evidence for vedolizumab and tofacitinib; low-quality evidence for golimumab and ustekinumab – Agreement rate: 100%)
- For adults with moderate to severe, active UC refractory to conventional therapy who are naïve to biologics, IG-IBD suggests using infliximab over adalimumab and golimumab for the induction of remission. (Conditional recommendation; very low-quality evidence – Agreement rate: 100%)
- For adults with moderate to severe UC refractory to conventional therapy who are naïve to biologics, IG-IBD suggests using vedolizumab over adalimumab due to vedolizumab's superiority in maintaining remission. (Conditional recommendation; low-quality evidence for induction of remission; moderate-quality evidence for maintenance of remission – Agreement rate: 82%)
- For adults with moderate to severe UC refractory to at least one anti-TNF agent, IG-IBD suggests against using adalimumab or vedolizumab to induce remission. (Conditional recommendation; low-quality evidence - Agreement rate: 45%)
- For adults with moderate to severe UC refractory to at least one biologic, IG-IBD recommends using tofacitinib or ustekinumab for the induction of remission. (Strong recommendation; moderate-quality evidence for tofacitinib; low-quality evidence for ustekinumab – Agreement rate: 91%)

1.2.7 Management of Pediatric Ulcerative Colitis, Ambulatory Care-An Evidence-based Guideline from European Crohn's and Colitis Organization and European Society of Pediatric Gastroenterology, Hepatology and Nutrition (2018)

The European Crohn's and Colitis Organization and the European Society of Pediatric Gastroenterology, Hepatology and Nutrition published their joint guidelines for the

management of pediatric UC in the **ambulatory** setting. The main recommendations are listed below[18]:

- Oral 5-ASA compounds are recommended as first-line induction and maintenance therapy for mild-moderate UC. (100% agreement)
- Combined oral and rectal 5-ASA therapy is more effective than oral 5-ASA monotherapy. (98% agreement)
- When rectal therapy is used, 5-ASA is preferred over steroids. (100% agreement)
- Oral steroids should be used as second-line treatment for mild-moderate UC not responding to 5- ASA (oral rectal) and may be considered as first line in the higher end of the moderate disease range. (100% agreement)
- Severe UC should normally be treated with intravenous steroids. (98% agreement)
- Second-generation oral steroids with lower systemic effect such as beclomethasone dipropionate (BDP) and budesonide-MMX (the evidence for budesonide-MMX is supportive only for left-sided colitis) may be considered in patients with mild disease refractory to 5-ASA before oral prednisolone. (93% agreement)
- Steroids are not recommended for maintaining remission; steroid sparing strategies should be applied. (100% agreement)
- Thiopurines are recommended for maintaining remission in children who are corticosteroid-dependent or relapsing frequently (>2 relapses per year) despite optimal 5-ASA treatment and in 5-ASA intolerant patients.
- Thiopurines should not be used for induction of remission in pediatric UC patients. (100% agreement)
- Infliximab (IFX) should be considered in chronically active or steroid-dependent UC, uncontrolled by 5- ASA and thiopurines, for both induction and maintenance of remission. (100% agreement)
- Adalimumab or golimumab could be considered in those who initially respond but then lose response or are intolerant to IFX, based on serum levels and antibodies. (95% agreement)
- Adalimumab and golimumab have no role in patients with primary non-response to IFX. (93% agreement)
- Vedolizumab should be considered in chronically active or steroid-dependent patients as a second-line biologic therapy after anti-TNF failure. (95% agreement)

1.2.8 Management of Pediatric Ulcerative Colitis, Part 2: Acute Severe Colitis—An Evidence-based Consensus Guideline from the European Crohn's and Colitis Organization and the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (2018)

The same organization issued a part 2 for ulcerative colitis pertaining to the management of **severe** ulcerative colitis. The recommendations for severe acute ulcerative colitis in the pediatric population are listed below[19]:

- Bacterial causes for ASC should be excluded by a stool culture including Clostridium difficile toxins A and B. (100% agreement).

Pain management:

- Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided in ASC. (98% agreement).
- Opiates should be used exceptionally with caution and close monitoring, in doses equivalent to 0.1 mg/ kg morphine, given the remote risk of facilitating megacolon (98% agreement).

Nutritional support:

- Regular diet should be continued in most ASC cases. Enteral (or parenteral in those not tolerating enteral) nutrition may be used if oral feeding is not tolerated or in malnutrition (98% agreement).
- Oral or enteral feeding is contraindicated in cases of megacolon, or when surgery is imminent (100% agreement).
- All mesalamine preparations (oral and rectal) should be discontinued upon admission to exclude mesalamine intolerance, especially when mesalamine has been commenced during the preceding few weeks; (re-) introduction should be considered after significant improvement in the clinical condition (100% agreement).
- Antibiotics are not routinely recommended in children with ASC at admission. Empiric antibiotic treatment may, however, be considered when C difficile or other bacterial infection is suspected until stool analysis is available (100% agreement).
- Intravenous methylprednisolone 1 mg/k/day (up to 40 mg/day) once daily in the morning is recommended as the initial treatment at admission; a higher dose of 1.5 mg/k/day (up to 60 mg/day) in 1 or 2 divided daily doses should be reserved to the more severe end of the spectrum and for children who have failed oral steroids before admission (100% agreement).

- The initial management of toxic megacolon includes, in addition to IVCS, intravenous fluid resuscitation, intravenous antibiotics (covering Gram-negative and anaerobic bacteria, eg, ampicillin, gentamycin, and metronidazole), bowel rest, and preparation for surgery. Insertion of a nasogastric tube, and rectal decompression tube as well as positional changes have been used in adults, but supportive evidence is absent in children. Oral vancomycin may be considered until the C difficile status is known (100% agreement).
- Cyclosporine, tacrolimus, and anti-TNFs are not recommended in the routine management of toxic megacolon, although several successful case reports have been published (100% agreement).

Table 7. Pediatric Ulcerative Colitis Activity Index (PUCAI)

Item		Points
1. Abdominal Pain	No pain	0
	Pain can be ignored	5
	Pain cannot be ignored	10
2. Rectal Bleeding	None	0
	Small amount only, in < 50% of stools	10
	Small amount with most stools	20
	Large amount (> 50% of the stool content)	30
3. Stool Consistency of Most Stools	Formed	0
	Partially formed	5
	Completely unformed	10
4. Number of Stools per 24 Hours	0 – 2	0
	3 – 5	5
	6 – 8	10
	> 8	15
5. Nocturnal Stools	No	0
	Yes	10
6. Activity Level	No limitation of activity	0
	Occasional limitation of activity	5
	Severe restricted activity	10

- A PUCAI >45 points on the third day of IVCS treatment should dictate planning for second-line therapy between days 3 to 5. (100% agreement).
- Second-line therapy should be initiated on the fifth day of IVCS treatment in children with a PUCAI >65 points (100% agreement).
- IVCS should be continued for an additional 2 to 5 days in children with a PUCAI of 35 to 65 on day 5; daily monitoring for confirming gradual response is recommended before a decision on second-line therapy is made in most cases within a total of 7 to 10 days of treatment (100% agreement).

<u>When steroids fail- medical second-line therapies:</u>

- Infliximab is recommended as the second-line medical therapy for anti-TNF naive children failing IVCS (100% agreement).
- Calcineurin inhibitors (tacrolimus and cyclosporine) can be considered as an alternative second-line medical therapy (100% agreement).
- When introducing second-line therapy, the possibility of non-response and therefore need for colectomy must always be discussed (100% agreement).

<u>Third line and sequential medical therapy:</u>

- In general, prompt referral for urgent colectomy is recommended following failure of 1 second-line medical therapy (95% agreement).

<u>Discharge recommendations:</u>

- Children should not be discharged from hospital unless the disease is at most mild (i.e., PUCAI <35 points) but preferably closer to remission (i.e., PUCAI <10 points) (98% agreement).
- Thiopurine maintenance is generally recommended after ASC responsive to IVCS; exclusive mesalamine maintenance therapy could be considered if a response to steroids has been rapid, and the patient was mesalamine naive before admission. (100% agreement).
- Patients responding to infliximab commenced during ASC should continue this drug as a maintenance treatment post discharge. (100% agreement).

Section 2.0 Drug Therapy

This section comprises four subsections: the first contains the newly recommended SFDA registered drugs, the second covers drug modifications, the third one outlines drugs that have been withdrawn from the market, and the fourth details new drugs that are not SFDA registered but FDA/EMA approved.

2.1 Additions

After January 2020, two new drugs have received FDA and EMA approval and are SFDA registered. This section will include all characteristics describing Ustekinumab and Upadacitinib as well as a health technology assessment (HTA) by major international bodies.

2.1.1 Ustekinumab

The following table describes the characteristics of drug ustekinumab[23–25]:

Table 8. Drug Therapy with Ustekinumab

SCIENTIFIC NAME USTEKINUMAB	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	K51
Drug Class	IMMUNOSUPRESSANT
Drug Sub-class	MONOCLONAL ANTIBODY
ATC Code	L04AC05
Pharmacological Class (ASHP)	Interleukin Inhibitor
DRUG INFORMATION	
Dosage Form	Solution for injection in pre-filled syringe
Route of Administration	Subcutaneous use
Dose (Adult) [DDD]*	Induction: IV: ≤55 kg: 260 mg as single dose. >55 kg to 85 kg: 390 mg as single dose. >85 kg: 520 mg as single dose.

	Maintenance: SUBQ: 90 mg every 8 weeks; begin maintenance dosing 8 weeks after the IV induction dose.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	**For Inflammatory bowel disease, moderate to severe; refractory:** Limited data available: Dosing varies by route of administration (IV or SUBQ); use extra caution. Children ≥12 years and Adolescents: Induction: <55 kg: IV: 260 mg as single dose. ≥55 to 85 kg: IV: 390 mg as single dose. >85 kg: IV: 520 mg as single dose. Maintenance: SUBQ: 90 mg every 8 weeks; begin maintenance dosing 8 weeks after the IV induction dose.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).
Prescribing edits*	AGE, MD, PA, ST
AGE (Age Edit): Only approved for ulcerative colitis in adults: for the pediatric population (<18 years) it has limited data available for refractory inflammatory bowel disease.	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Only physicians experienced in immunosuppressive therapy and management of UC, Crohn disease or psoriasis.	
PA (Prior Authorization): Only prescribed to adults with moderately active UC who have failed conventional therapy or for induction and maintenance of remission in patients with moderate-to-severely active UC at a dose of 90mg every 8 weeks for maintenance therapy and weight based for induction therapy and requires specific gastroenterologist request process.	
QL (Quantity Limit): N/A	
ST (Step Therapy): In patients with moderately active UC who have failed conventional therapy.	
EU (Emergency Use Only): N/A	

PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** nasopharyngitis, headache, abdominal pain, diarrhea, nausea and vomiting **Most serious**: hypersensitivity reactions including anaphylaxis
Drug Interactions*	**Category X**: • Abrocitinib • Anifrolumab • Baricitinib • BCG Products • Brivudine • Cladribine • Dengue Tetravalent Vaccine (Live) • Deucravacitinib • Filgotinib • InFLIXimab • Mumps- Rubella- or Varicella Containing Live Vaccines • Nadofaragene Firadenovec • Natalizumab • Pimecrolimus • Poliovirus Vaccine (Live/Trivalent/Oral) • Ruxolitinib (Topical) • Tacrolimus (Topical) • Talimogene Laherparepvec • Tertomotide • Tofacitinib • Typhoid Vaccine • Upadacitinib • Vaccines (Live) • Yellow Fever Vaccine
Special Population	Patients >100 kg: May require higher dose to achieve adequate serum levels.
Pregnancy	Ustekinumab crosses the placenta. Fetal exposure is dependent upon the IgG subclass, maternal serum concentrations, placental integrity, newborn birth weight, and GA,

	generally increasing as pregnancy progresses. The lowest exposure would be expected during the period of organogenesis and the highest during the third trimester.
Lactation	Ustekinumab is present in breast milk. The use of ustekinumab during human lactation is very limited.
Contraindications	US labeling: Clinically significant hypersensitivity to ustekinumab or any component of the formulation. Canadian labeling: Severe infections such as sepsis, tuberculosis, and opportunistic infections
Monitoring Requirements	Obtain CBC with differential (baseline); complete metabolic panel (baseline); tuberculosis (TB) screening prior to initiating and during therapy (chest X-ray if TB positive); hepatitis C virus/hepatitis B virus (HBV) screening prior to initiating (all patients), HBV carriers (during and for several months following therapy); HIV screening (baseline).
Precautions	-Antibody formation -Hypersensitivity reactions→ Discontinue immediately with signs/symptoms of hypersensitivity reaction and treat appropriately as indicated. -Infections: May increase the risk for infections or reactivation of latent infections → Avoid use in patients with clinically important active infection until the infection resolves or is successfully treated. Exercise caution when considering use in patients with a history of new/recurrent infections, with conditions that predispose them to infections (e.g., diabetes or residence/travel from areas of

	endemic mycoses), with chronic, latent, or localized infections. -Malignancy: May increase the risk for malignancy although the impact on the development and course of malignancies is not fully defined. → Monitor all patients closely for the development of nonmelanoma skin cancer; closely follow patients >60 years of age, with a history of prolonged immunosuppression, and in patients with a history of PUVA treatment. -Noninfectious pneumonia → Discontinue therapy and institute appropriate treatment if noninfectious pneumonia is suspected or confirmed. -Posterior reversible encephalopathy syndrome → discontinue therapy immediately if symptoms occur and administer appropriate therapy. -Tuberculosis: Do not use in patients with active tuberculosis (TB) → Consider antituberculosis treatment in patients with a history of latent or active tuberculosis if an adequate prior treatment course cannot be confirmed.
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

Table 6 lists the HTA recommendations for Ustekinumab by the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH) and the Pharmaceutical Benefits Advisory Committee (PBAC) in the management of US.

Table 9. Ustekinumab HTA Recommendations

Medication	Agency	Date – HTA Recommendation
Ustekinumab	CADTH[8]	2020: The CADTH Canadian Drug Expert Committee recommends that ustekinumab be reimbursed for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with lost response to or were intolerant to either conventional therapy or a biologic, or have medical contraindications to such therapies, only if the following conditions are met. Conditions for Reimbursement: Renewal Criteria: The patient must have achieved clinical response to induction therapy within eight weeks for reimbursement of treatment with ustekinumab to continue to maintenance therapy. Prescribing Conditions: The prescribing of ustekinumab for the treatment of ulcerative colitis should be restricted to gastroenterologists. Pricing Conditions: The drug plan cost of treatment with ustekinumab should not exceed the drug plan cost of the least costly biologic currently reimbursed for the treatment of ulcerative colitis.
	NICE[9]	2020: Ustekinumab is recommended for people who cannot have TNF-alpha inhibitors. When ustekinumab is compared with vedolizumab, for all scenarios investigated and irrespective of the source of utilities, the ICERs are below £30,000 per QALY gained for both patient subgroups (failed conventional therapy with or without prior exposure to a biological). Therefore, the committee agreed that ustekinumab is likely to be a cost-effective use of NHS resources in people who would otherwise have vedolizumab.
	PBAC[10]	2022: The PBAC recommended the Section 100 (Highly Specialized Drugs Program) and General Schedule listings of ustekinumab (UST) for the treatment of

		moderate to severe ulcerative colitis (MSUC). The PBAC noted the recommendation for Section 100 was for intravenous (IV) induction dosing at initiation, and General Schedule listing was for subcutaneous injection for subsequent dosing. The PBAC's recommendation for listing was based on its assessment that the cost-effectiveness of UST would be acceptable if it were cost minimized to the least costly alternative therapy of infliximab (IFX), tofacitinib (TOF), vedolizumab (VDZ) and golimumab (GOL). The PBAC accepted that UST is likely of non-inferior comparative effectiveness and safety to these agents in MSUC and considered there is sufficient evidence to conclude that UST, for some patients, provides a significant improvement in efficacy in the induction phase compared to adalimumab (ADA).
	HAS[11]	2020: Considering: • the demonstration of the superiority of ustekinumab compared to placebo in induction treatment (a single intravenous injection of approximately 6 mg/kg infusion) on clinical remission at 8 weeks and in maintenance treatment (90 mg subcutaneously every 8 or 12 weeks) on clinical remission at 44 weeks in adults with moderate to severe active UC who have failed conventional treatment or at least one biological drug (anti-TNFa and/or vedolizumab), • the demonstration of superiority of ustekinumab compared to placebo on histoendoscopic healing in induction treatment but not in maintenance treatment, • the lack of direct comparison to drugs available in 3rd line treatment (vedolizumab, tofacitinib or even an anti-TNF), STELARA 45 mg, 90 mg, and 130 mg (ustekinumab) do not provide any improvement in actual benefit (ASMR V) in the treatment of moderate to severe active ulcerative colitis in adults, in the event of failure (response insufficient, loss of response, intolerance or contraindication) of conventional treatments (5-

		aminosalicylates, corticosteroids and immunosuppressants) and of at least one biological medicine among anti-TNFa and vedolizumab.
	IQWIG	N/A

Conclusion Statement – Ustekinumab

Ustekinumab is recommended for adults with moderately active UC who have failed conventional therapy. HTA analysis supported the use of ustekinumab in the treatment of UC. It should be noted that only gastroenterologists are allowed to prescribe it. Ustekinumab has multiple drug-drug interactions, and caution should be applied when prescribing, with a thorough screening of the patient's prior medication use.

2.1.2 Upadacitinib

Table 7 describes the characteristics of upadacitinib[26–28]:

Table 10. Drug Therapy with Upadacitinib

SCIENTIFIC NAME UPADACITINIB	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	K51
Drug Class	IMMUNOSUPRESSANT
Drug Sub-class	JANUS KINASE (JAK) INHIBITORS
ATC Code	L04AA
Pharmacological Class (ASHP)	Janus Kinase (Jak) Inhibitors
DRUG INFORMATION	
Dosage Form	Prolonged-release tablet
Route of Administration	Oral use
Dose (Adult) [DDD]*	Induction: 45 mg once daily for 8 weeks. Maintenance: 15 mg once daily; may increase to 30 mg once daily in patients with refractory, severe, or extensive disease.

	Discontinue if an adequate response is not achieved with the 30 mg dose; use the lowest effective dose needed to maintain response.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	Altered kidney function: eGFR ≥30 mL/minute/1.73 m2: No dosage adjustment necessary. eGFR 15 to <30 mL/minute/1.73 m2: Induction: 30 mg once daily for 8 weeks Maintenance: 15 mg once daily. eGFR <15 mL/minute/1.73 m2: Use is not recommended. Liver impairment: Mild to moderate impairment (Child-Pugh class A or B): Induction: 30 mg once daily for 8 weeks Maintenance: 15 mg once daily. Severe impairment (Child-Pugh class C): Use is not recommended. Hepatotoxicity during treatment: Treatment should be interrupted if drug-induced liver injury is suspected. Toxicity: Hematologic: Absolute lymphocyte count (ALC) <500/mm3: Interrupt therapy until ALC ≥500/mm3. ANC <1,000/mm3: Interrupt therapy until ANC ≥1,000/mm3.

	<u>Hemoglobin <8 g/dL:</u> Interrupt therapy until hemoglobin ≥8 g/dL. <u>Infection (serious):</u> Interrupt treatment until the infection is controlled.
Prescribing edits*	AGE, MD, PA, ST
AGE (Age Edit): Only approved for UC in adults. Upadacitinib is not recommended for use in children and adolescents under 18 years of age because it has not been studied.	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Only physicians experienced in immunosuppressive therapy and management of UC, Crohn disease, rheumatoid arthritis, psoriasis, spondylitis, or dermatitis.	
PA (Prior Authorization): Only prescribed to adults for induction and maintenance of remission in UC following failure of conventional and/or advanced therapies at a dose of 45mg once daily for 8 weeks followed by 15mg once daily for maintenance and requires specific gastroenterologist request process.	
QL (Quantity Limit): N/A	
ST (Step Therapy): Use upadacitinib for induction and maintenance of remission in UC following failure of conventional and/or advanced therapies.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**<u>Most common</u>**: throat, nose infections, acne, non-melanoma skin cancer, cough, fever, low white blood cell counts, weight gain, anaemia, urinary tract infection and rash **<u>Most serious</u>**: Infections, pneumonia, which may cause shortness of breath, fever, and a cough with mucus, sepsis, allergic reaction (chest tightness, wheezing, swelling of the lips, tongue or throat, hives)
Drug Interactions*	**<u>Category X</u>**: • Abrocitinib • Anifrolumab

	• Baricitinib • BCG intravesical • BCG Products • Brivudine • Cladribine • CYP3A4 inducers (strong) • Dengue Tetravalent Vaccine (Live) • Deucravacitinib • Dipyrone • Fexinidazole • Filgotinib • Fusidic acid • Grapefruit juice • Immunosuppressants (Cytotoxic Chemotherapy) • Immunosuppressants (Miscellaneous Oncologic Agents) • Immunosuppressants (Therapeutic Immunosuppressant Agents) • Mumps- Rubella- or Varicella Containing Live Vaccines • Nadofaragene Firadenovec • Natalizumab • Pimecrolimus • Poliovirus Vaccine (Live/Trivalent/Oral) • Ruxolitinib (Topical) • Tacrolimus (Topical) • Talimogene Laherparepvec • Tertomotide • Tofacitinib • Typhoid Vaccine • Upadacitinib • Vaccines (Live) • Yellow Fever Vaccine • Zavegepant
Special Population	Older adults: 65 years of age or older, the recommended dose is 15 mg once a day for long-term. treatment.

Pregnancy	Upadacitinib must not be used during pregnancy
Lactation	Do not use upadacitinib while breast-feeding as it is not known if this medicine passes into breast milk.
Contraindications	Hypersensitivity to upadacitinib or any component of the formulation.
Monitoring Requirements	Lymphocyte count, neutrophil count, hemoglobin, and LFTs (baseline and periodically thereafter); lipids (12 weeks after therapy initiation and periodically thereafter); viral hepatitis (prior to initiating therapy and periodically thereafter); latent and active tuberculosis (TB) screen at baseline; verify pregnancy status (prior to initiating therapy); signs/symptoms of infection (including TB) during and after therapy; skin examinations (periodically, in patients at increased risk for skin cancer); symptoms of thrombosis.
Precautions	-GI perforation → use with caution in patients at increased risk for GI perforation -Hematologic toxicity → do not initiate therapy in patients with an absolute lymphocyte count <500/mm3, ANC <1,000/mm3, or hemoglobin <8 g/dL. Monitor CBC at baseline and periodically thereafter. -Hepatic effects → monitor LFTs at baseline and periodically thereafter; interrupt therapy if LFTs increased and drug-induced liver injury is suspected. -Lipid abnormalities: Increased lipid parameters → assess lipids 12 weeks after upadacitinib initiation and manage lipid abnormalities according to current clinical guidelines.

	-Medication residue in stool → monitor patients for clinical response and consider alternative therapy if there is a lack of therapeutic response. -Tuberculosis → Use with caution in patients who have resided or traveled in regions where TB is endemic.
Black Box Warning	- Serious infections - Mortality - Malignancies - MACE - Thrombosis
REMS*	N/A

Health Technology Assessment (HTA)

Table 8 lists the HTA recommendations for Upadacitinib by the National Institute for Health and Care Excellence (NICE) in 2023. Others HTA bodies do not tackle UC as the indication of interest.

Table 11. Upadacitinib HTA Recommendations

Mediation	Agency	Date – HTA Recommendation
Upadacitinib	CADTH[29]	In process
	NICE[12]	2023: Looking at the cost-effectiveness results, upadacitinib had the greatest net health benefit suggesting that it is a cost-effective use of NHS resources compared with existing NICE recommended treatments. However, the committee noted that the differences between costs and QALYs were very small. The committee agreed it was likely that upadacitinib is a cost-effective use of NHS resources when conventional or biological treatments are not tolerated or are not working well enough. The committee concluded that upadacitinib is considered cost effective for treating moderately to severely active ulcerative colitis.
	PBAC[13]	2023: The PBAC recommended the General Schedule, Authority Required (in writing) listing of upadacitinib (UPA) for the treatment moderate to severe ulcerative colitis (MSUC). The PBAC's recommendation for listing

		was based on, among other matters, its assessment that the cost-effectiveness of UPA would be acceptable if it were cost minimized to the least costly alternative therapy out of infliximab (IFX), tofacitinib (TOF), vedolizumab (VDZ), ustekinumab (UST) and golimumab (GOL). The PBAC noted the clinical claim was that UPA was of superior comparative effectiveness to all currently listed b/ts DMARDs in induction therapy and of non-inferior comparative to GOL, TOF and VDZ in maintenance therapy. The PBAC noted a clinical effectiveness claim was not made versus ADA or IFX in maintenance therapy due to differences in the clinical trial designs. The PBAC considered, based on the evidence presented, that UPA is likely to be of non-inferior comparative effectiveness and safety to these agents in MSUC and considered there is also likely sufficient evidence that UPA, for some patients, provides a significant improvement in effectiveness in the induction phase compared to adalimumab (ADA).
	HAS[14]	2023: Considering: • the methodological quality of the pivotal studies (controlled, randomised, double-blind, relevant choices of outcome measures including quality of life, sample size), but given that the choice of placebo is regrettable in particular for biological treatment-naive patients, and the efficacy was assessed in a heterogenous population including biological treatment-naive and non-naive patients; • the evidence of superiority of upadacitinib versus placebo, with a relevant effect size both in the induction phase and maintenance phase; the lack of evidence of an effect on referral for colectomy; • the lack of comparative data versus TNFα inhibitors in patients exhibiting a poor response to a conventional basic treatment and TNFα inhibitor-naive, and versus vedolizumab (ENTYVIO), while these comparisons were possible;

		• and the safety profile of upadacitinib; The Transparency Committee deems that RINVOQ (upadacitinib) provides no clinical added value (CAV V) in the therapeutic strategy of adult ulcerative colitis.
	IQWIG	Not available

Conclusion Statement – Upadactinib

Upadacitinib is recommended for adults for induction and maintenance of remission in UC following failure of conventional and/or advanced therapies. HTA analysis in NICE and PBAC showed that upadacitinib is cost-effective for the treatment of ulcerative colitis. CADTH HTA analysis is under process. HAS showed that there is no clinical added value for the use of upadacitinib. It should be noted that only gastroenterologists are allowed to prescribe it. Always make sure of the drugs used concomitantly with upadacitinib since the list of interactions is long.

2.2 Modifications

Some modifications were made to the previous 2020 CHI report.

1. Please refer to section 2.3.6 in the previous report to highlight these modifications:

Azathioprine does not need “Prior Authorization (PA)” and “Emergency Use (EU)” as prescribing edits. It is used as an adjunctive therapy and can be administered orally. Make sure of the side effects[30].

2. Please refer to section 3.3(b).7 in the previous report to highlight this modification:

A “Step Therapy (ST)” prescribing edit was added for cyclosporine: it should be used in hospitalized adult patients with acute severe ulcerative colitis refractory to intravenous corticosteroids, the AGA suggests using infliximab or cyclosporine[15].

3. Please refer to section 3.5.9 in the previous report to highlight this modification:

A “ST” prescribing edit for budesonide: it may be considered in patients with mild disease refractory to 5-ASA before oral prednisolone[15].

4. Please refer to section 2.5.8 in the previous report to highlight this modification:

A “ST” prescribing edit was added for tofacitinib: it should be considered as a second-line treatment in adult outpatients with moderate-to-severe UC who failed biologic agents[15].

2.3 Delisting

There are no withdrawn drugs for UC.

2.4 Other Drugs

2.4.1 Ozanimod

FDA approved ozanimod for ulcerative colitis on May 27, 2021[31].

EMA approves ozanimod for ulcerative colitis on October 14, 2021[32].

According to the 2022 Saudi Arabia Consensus Guidance for the Diagnosis and Management of Adults with Inflammatory Bowel Disease, ozanimod is used for induction and maintenance of remission in UC following failure of conventional and/or advanced therapies. Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed)[15].

The recommended dose used is: Oral: Initial: 0.23 mg once daily on days 1 through 4, then 0.46 mg once daily on days 5 through 7; maintenance dose: 0.92 mg once daily starting on day 8[33].

2.4.2 Etrasimod

Etrasimod, an oral sphingosine 1-phosphate (S1P) receptor modulator, is under investigation for treating adults with moderate to severe ulcerative colitis. The FDA and EMA accepted Etrasimod regulatory submissions for ulcerative colitis. in December 2022[34].

Etrasimod 2 mg once daily on clinical remission in UC patients who had previously failed or were intolerant to at least one conventional, biologic, or Janus kinase (JAK) inhibitor therapy.

This recommendation is based on the **ELEVATE UC 52 trial**, which is a randomized, double-blind, placebo-controlled trial that utilizes a treat-through design comprising of a 12-week induction period followed by a 40-week maintenance period. Beginning at week 12, all patients could continue their randomized treatment. The primary objective of this trial was to assess the safety and efficacy of etrasimod 2 mg once daily on clinical remission after both 12 and 52 weeks. The primary endpoint is based on the 3-domain, modified Mayo score (MMS). Clinical remission was 27.0% for patients receiving etrasimod compared to 7.4% for patients receiving placebo at week 12 (19.8% differential, P≤.001) and was 32.1% compared to 6.7% at week 52 (25.4% differential, P≤.001). Statistically significant improvements were attained in all key secondary endpoints, including endoscopic improvement, symptomatic remission, and mucosal

healing at weeks 12 and 52, and corticosteroid-free remission and sustained clinical remission at week 52[34].

Section 3.0 Key Recommendations Synthesis

- In patients with moderately active UC who have failed conventional therapy, treatment with biological therapies, i.e., infliximab, golimumab, adalimumab, vedolizumab, or **ustekinumab** is recommended. Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed)[15].
- Using **ustekinumab** for induction and maintenance of remission in patients with moderate-to-severely active UC is recommended. Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed)[15].
- Using **upadacitinib** for induction and maintenance of remission in UC following failure of conventional and/or advanced therapies is recommended. Quality of evidence: High; GRADE: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed)[15].
- Infliximab, golimumab, adalimumab, vedolizumab, **ustekinumab**, ozanimod, **upadacitinib**, or tofacitinib for UC patients on high-dose 5-ASA maintenance therapy requiring two or more courses of corticosteroids in the preceding year or who developed corticosteroid dependence or refractory condition is recommended. Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed)[15].
- If disease relapse occurs with **ustekinumab** therapy, dose escalation (typically by decreasing the dosing interval to every 4 weeks) should be considered while evaluating for co-existing or exacerbating factors. Quality of evidence: Moderate; Grade: Moderate. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed)[15].

Management of hospitalized patients:

In hospitalized adult patients with acute severe ulcerative colitis, the AGA suggests using intravenous methylprednisolone dose equivalent of 40 to 60mg/d rather than higher dose intravenous corticosteroids. (Conditional recommendation, very low-quality evidence)[16].

In hospitalized adult patients with acute severe ulcerative colitis refractory to intravenous corticosteroids, the AGA suggests using infliximab or cyclosporine. (Conditional recommendation, low quality evidence)[16].

For pediatric ulcerative colitis- ambulatory care:

Oral 5-ASA compounds are recommended as first-line induction and maintenance therapy for mild-moderate UC. (100% agreement)[18].

Thiopurines are recommended for maintaining remission in children who are corticosteroid-dependent or relapsing frequently (>2 relapses per year) despite optimal 5-ASA treatment and in 5-ASA intolerant patients[18].

Infliximab (IFX) should be considered in chronically active or steroid-dependent UC, uncontrolled by 5- ASA and thiopurines, for both induction and maintenance of remission. (100% agreement)[18].

Adalimumab or golimumab could be considered in those who initially respond but then lose response or are intolerant to IFX, based on serum levels and antibodies. (95% agreement)[18].

Vedolizumab should be considered in chronically active or steroid-dependent patients as a second-line biologic therapy after anti-TNF failure. (95% agreement)[18].

For pediatric patients with severe acute colitis:

- A PUCAI > 45 points on the third day of IVCS treatment should dictate planning for second-line therapy between days 3 to 5. (100% agreement)[19].
- Second-line therapy should be initiated on the fifth day of IVCS treatment in children with a PUCAI >65 points (100% agreement)[19].
- IVCS should be continued for an additional 2 to 5 days in children with a PUCAI of 35 to 65 on day 5; daily monitoring for confirming gradual response is recommended before a decision on second-line therapy is made in most cases within a total of 7 to 10 days of treatment (100% agreement)[19].

<u>When steroids fail- medical second-line therapies:</u>

- Infliximab is recommended as the second-line medical therapy for anti-TNF naive children failing IVCS (100% agreement)[19].
- Calcineurin inhibitors (tacrolimus and cyclosporine) can be considered as an alternative second-line medical therapy (100% agreement)[19].
- When introducing second-line therapy, the possibility of non-response and therefore need for colectomy must always be discussed (100% agreement)[19].

<u>Third line and sequential medical therapy:</u>

- In general, prompt referral for urgent colectomy is recommended following failure of 1 second-line medical therapy (95% agreement)[19].

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Ulcerative colitis report** and aims to provide recommendations to aid in the management of ulcerative colitis. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Ulcerative colitis. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. Ulcerative Colitis Scope

Section	Rationale/Updates
	Saudi Arabia consensus guidance for the diagnosis and management of adults with inflammatory bowel disease 2022 [15] In individuals suspected of having UC, stool testing is recommended to rule out enteric infections, including special testing for Clostridioides difficile (C. diff) infection. Quality of evidence: High; Grade: High Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).

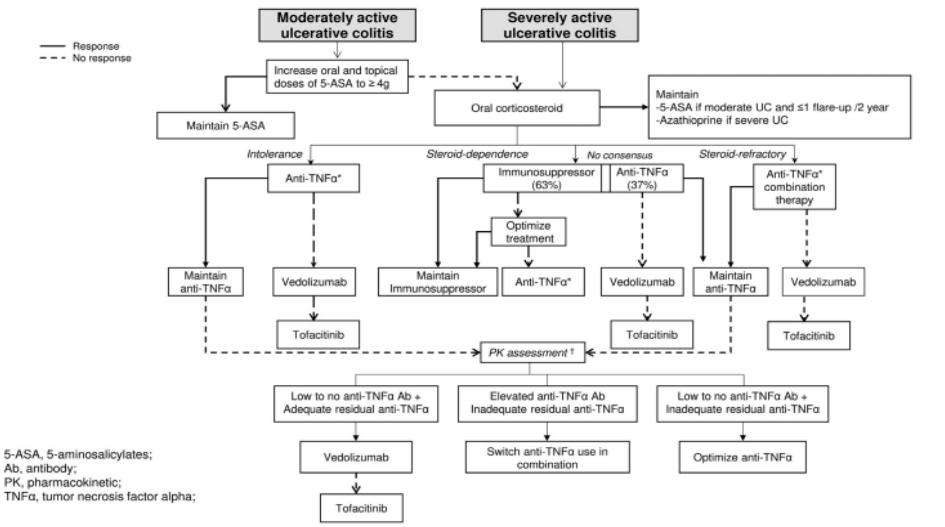
	Before starting any biologic therapy, including anti-TNF treatment, patients with IBD must be screened for latent TB using chest radiography and a purified protein derivative (PPD) skin test and/or an IGRA. Quality of evidence: High; Grade: High Strength of recommendation: Very strongly recommended (100% of panel strongly agreed). The conventional "step-up" approach is the core approach for the treatment of UC, except for patients who present with acute severe ulcerative colitis (ASUC) that requires hospitalization. Quality of evidence: High; Grade: High Strength of recommendation: Very strongly recommended (100% of panel strongly agreed). Oral and/or topical 5-ASA derivatives are recommended as first-line treatment for the induction and maintenance of remission in mild-to-moderate UC. Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed). Budesonide MMX topical and/or systemic corticosteroids are recommended for induction of remission in UC, in patients who failed to respond to mesalazine derivatives. Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed). Oral budesonide MMX is recommended over conventional oral corticosteroids to induce remission in UC. If conventional oral corticosteroids are used, the patient should be advised about common and serious side effects of corticosteroids. Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed). We recommend using thiopurines to maintain remission in patients with UC who are corticosteroid resistant or corticosteroid dependent. Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed). We recommend using vedolizumab over adalimumab to induce remission in moderate-to-severe ambulatory UC patients naïve to biologic agents. Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed). We recommend using, in patients with moderately active UC who have failed conventional therapy, treatment with biological

	therapies, i.e., infliximab, golimumab, adalimumab, vedolizumab, or ustekinumab, is recommended. Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed). We recommend using ustekinumab for induction and maintenance of remission in patients with moderate-to-severely active UC. Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed). We recommend using ozanimod for induction and maintenance of remission in UC following failure of conventional and/or advanced therapies. Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed). We recommend using upadacitinib for induction and maintenance of remission in UC following failure of conventional and/or advanced therapies. Quality of evidence: High; GRADE: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed). We recommend using tofacitinib as a second-line treatment in adult outpatients with moderate-to-severe UC who failed biologic agents. Quality of evidence: High; Grade: High. Strength of recommendation: Strongly recommended (60% of panel strongly agreed). We do “not” recommend using tofacitinib for patients with a history of thromboembolic disease, cardiovascular disease, or those ≥50 years old, with at least one cardiovascular risk factor, because of an increased risk of thromboembolic events. Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed). We recommend “against” methotrexate use to initiate or maintain remission in adults with moderate-to-severe UC. Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed). We recommend combining infliximab with thiopurines over infliximab monotherapy in moderate-to-severe UC. There is insufficient evidence to recommend combining other biologic therapies with thiopurines. Quality of evidence: Moderate; Grade:

	Moderate. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed). We recommend "against" 5-ASA continuation for maintenance of remission in adult ambulatory patients with moderate-to-severe UC who have attained remission with the use of immunosuppressants and/or biologic agents or tofacitinib. Quality of evidence: Moderate; Grade: Moderate. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed). We recommend infliximab, golimumab, adalimumab, vedolizumab, ustekinumab, ozanimod, upadacitinib, or tofacitinib for UC patients on high-dose 5-ASA maintenance therapy requiring two or more courses of corticosteroids in the preceding year or who developed corticosteroid dependence or refractory condition. Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed). We recommend considering vedolizumab for patients ≥65 years old, patients with a history of a recent infection, and individuals at higher risk of infection or malignancy. Quality of evidence: High; Grade: High. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed). If disease relapse occurs with vedolizumab therapy, dose escalation (by shortening dosing interval to every 4 weeks) should be considered while evaluating for co-existing or triggering factors. Quality of evidence: Moderate; Grade: Moderate. Strength of recommendation: Very strongly recommended (90% of panel strongly agreed). If disease relapse occurs with ustekinumab therapy, dose escalation (typically by decreasing the dosing interval to every 4 weeks) should be considered while evaluating for co-existing or exacerbating factors. Quality of evidence: Moderate; Grade: Moderate. Strength of recommendation: Very strongly recommended (100% of panel strongly agreed).
	American Gastroenterological Association Institute Clinical Guideline on the Management of Moderate to Severe Ulcerative Colitis 2020[16] In adult outpatients with moderate-severe ulcerative colitis, the AGA recommends using infliximab, adalimumab, golimumab,

	vedolizumab, tofacitinib or ustekinumab over no treatment. (Strong recommendation, moderate quality evidence) In adult outpatients with moderate-severe ulcerative colitis who are naïve to biologic agents, the AGA suggests using infliximab or vedolizumab rather than adalimumab, for induction of remission. (Conditional recommendation, moderate quality evidence) In adult outpatients with moderate-severe ulcerative colitis who have previously been exposed to infliximab, particularly those with primary non-response, the AGA suggests using ustekinumab or tofacitinib, rather than vedolizumab or adalimumab for induction of remission. (Conditional recommendation, low quality evidence) In adult outpatients with active moderate-severe ulcerative colitis, the AGA suggests against using thiopurine monotherapy for INDUCTION of remission. (Conditional recommendation, very low quality of evidence) In adult outpatients with moderate-severe ulcerative colitis in remission, the AGA suggests using thiopurine monotherapy, rather than no treatment, for MAINTENANCE of remission. (Conditional recommendation low quality of evidence) In adult outpatients with moderate-severe ulcerative colitis, the AGA suggests against using methotrexate monotherapy, for induction or maintenance of remission. (Conditional recommendation, low quality evidence) In adult outpatients with active moderate-severe ulcerative colitis, the AGA suggests using biologic monotherapy (TNFα antagonists, vedolizumab, ustekinumab) rather than thiopurine monotherapy for INDUCTION of remission. (Conditional recommendation, low quality evidence) In adult outpatients with moderate-severe ulcerative colitis in remission, the AGA makes no recommendation in favor of, or against, using biologic monotherapy (TNFα antagonists, vedolizumab or ustekinumab), rather than thiopurine monotherapy for MAINTENANCE of remission. (No recommendation, knowledge gap) In adult outpatients with moderate-severe ulcerative colitis, the AGA suggests combining TNFα antagonists, vedolizumab or ustekinumab with thiopurines or methotrexate, rather than biologic monotherapy. (Conditional recommendation, low quality evidence)

	In adult outpatients with moderate-severe ulcerative colitis, the AGA suggests combining TNFα antagonists, vedolizumab or ustekinumab with thiopurines or methotrexate, rather than thiopurine monotherapy. (Conditional recommendation, low quality evidence) In adult outpatients with moderate-severe ulcerative colitis, the AGA suggests early use of biologic agents with or without immunomodulator therapy, rather than gradual step up after failure of 5-aminosalicylates. (Conditional recommendation, very low-quality evidence) In adult outpatients with moderate-severe ulcerative colitis who have achieved remission with biologic agents and/or immunomodulators, or tofacitinib, the AGA suggests against continuing 5-aminosalicylates for induction and maintenance of remission. (Conditional recommendation, very low-quality evidence) <u>Management of hospitalized patients:</u> In hospitalized adult patients with acute severe ulcerative colitis, the AGA suggests using intravenous methylprednisolone dose equivalent of 40 to 60mg/d rather than higher dose intravenous corticosteroids. (Conditional recommendation, very low-quality evidence) In hospitalized adult patients with acute severe ulcerative colitis without infections, the AGA suggests against adjunctive antibiotics. (Conditional recommendation, very low quality of evidence) In hospitalized adult patients with acute severe ulcerative colitis refractory to intravenous corticosteroids, the AGA suggests using infliximab or cyclosporine. (Conditional recommendation, low quality evidence).
	Clinical guidelines for the management of inflammatory bowel disease: Update of a French national consensus 2020[22]

	
	Use of biologics and small molecule drugs for the management of moderate to severe ulcerative colitis: IG-IBD clinical guidelines based on the GRADE methodology 2022 [17] For adults with moderate to severe UC refractory to conventional therapy who are naïve to biologics, IG-IBD recommends using infliximab, adalimumab, golimumab, vedolizumab, ustekinumab or tofacitinib over no treatment to induce remission. (Strong recommendation; high-quality evidence for infliximab and adalimumab; moderate-quality evidence for vedolizumab and tofacitinib; low-quality evidence for golimumab and ustekinumab – Agreement rate: 100%) For adults with moderate to severe, active UC refractory to conventional therapy who are naïve to biologics, IG-IBD suggests using infliximab over adalimumab and golimumab for the induction of remission. (Conditional recommendation; very low-quality evidence – Agreement rate: 100%) For adults with moderate to severe UC refractory to conventional therapy who are naïve to biologics, IG-IBD suggests using vedolizumab over adalimumab due to vedolizumab's superiority in maintaining remission. (Conditional recommendation; low-quality evidence for induction of remission; moderate-quality evidence for maintenance of remission – Agreement rate: 82%) For adults with moderate to severe UC refractory to at least one anti-TNF agent, IG-IBD suggests against using adalimumab or vedolizumab to induce remission. (Conditional recommendation; low-quality evidence - Agreement rate: 45%)

	For adults with moderate to severe UC refractory to at least one biologic, IG-IBD recommends using tofacitinib or ustekinumab for the induction of remission. (Strong recommendation; moderate-quality evidence for tofacitinib; low-quality evidence for ustekinumab – Agreement rate: 91%)
	Management of Paediatric Ulcerative Colitis, Ambulatory Care- An Evidence-based Guideline from European Crohn's and Colitis Organization and European Society of Paediatric Gastroenterology, Hepatology and Nutrition 2018[18] Oral 5-ASA compounds are recommended as first-line induction and maintenance therapy for mild-moderate UC. (100% agreement) Combined oral and rectal 5-ASA therapy is more effective than oral 5-ASA monotherapy. (98% agreement) When rectal therapy is used, 5-ASA is preferred over steroids. (100% agreement) Oral steroids should be used as second-line treatment for mild-moderate UC not responding to 5- ASA (oral rectal) and may be considered as first line in the higher end of the moderate disease range. (100% agreement) Severe UC should normally be treated with intravenous steroids. (98% agreement) Second-generation oral steroids with lower systemic effect such as beclomethasone dipropionate (BDP) and budesonide-MMX(the evidence for budesonide-MMX is supportive only for left-sided colitis) may be considered in patients with mild disease refractory to 5-ASA before oral prednisolone. (93% agreement) Steroids are not recommended for maintaining remission; steroid sparing strategies should be applied. (100% agreement) Thiopurines are recommended for maintaining remission in children who are corticosteroid-dependent or relapsing frequently (>2 relapses per year) despite optimal 5-ASA treatment and in 5-ASA intolerant patients. Thiopurines should not be used for induction of remission in pediatric UC patients. (100% agreement) Measuring thiopurine metabolites is recommended in patients with incomplete response on a stable thiopurine dosage, in patients who present with leucopenia or elevated

	transaminases, or if poor compliance is suspected. (95% agreement) Infliximab (IFX) should be considered in chronically active or steroid-dependent UC, uncontrolled by 5- ASA and thiopurines, for both induction and maintenance of remission. (100% agreement) Adalimumab or golimumab could be considered in those who initially respond but then lose response or are intolerant to IFX, based on serum levels and antibodies. (95% agreement) Adalimumab and golimumab have no role in patients with primary non-response to IFX. (93% agreement) Vedolizumab should be considered in chronically active or steroid-dependent patients as a second-line biologic therapy after anti-TNF failure. (95% agreement)

Appendix C. MeSH Terms PubMed

Query		Filters	Search Details	Results
((((Colitis, Ulcerative [MeSH Major Topic]) OR (Idiopathic Proctocolitis [Title/Abstract])) OR (Ulcerative Colitis[Title/Abstract])) OR (Colitis Gravis[Title/Abstract])) OR (Inflammatory Bowel Disease, Ulcerative Colitis Type[Title/Abstract])		Guideline, in the last 5 years	("colitis, ulcerative"[MeSH Major Topic] OR "idiopathic proctocolitis"[Title/Abstract] OR "ulcerative colitis"[Title/Abstract] OR "colitis gravis"[Title/Abstract] OR "inflammatory bowel disease ulcerative colitis type"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline [Filter]))	41

Appendix D. Treatment Algorithm